(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
31 August 2006 (31.08.2006)

PCT

(10) International Publication Number
WO 2006/091567 A2

(51) International Patent Classification:
A61K 31/355 (2006.01)

(21) International Application Number:
PCT/US2006/006042

(22) International Filing Date:
22 February 2006 (22.02.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/655,495 23 February 2005 (23.02.2005) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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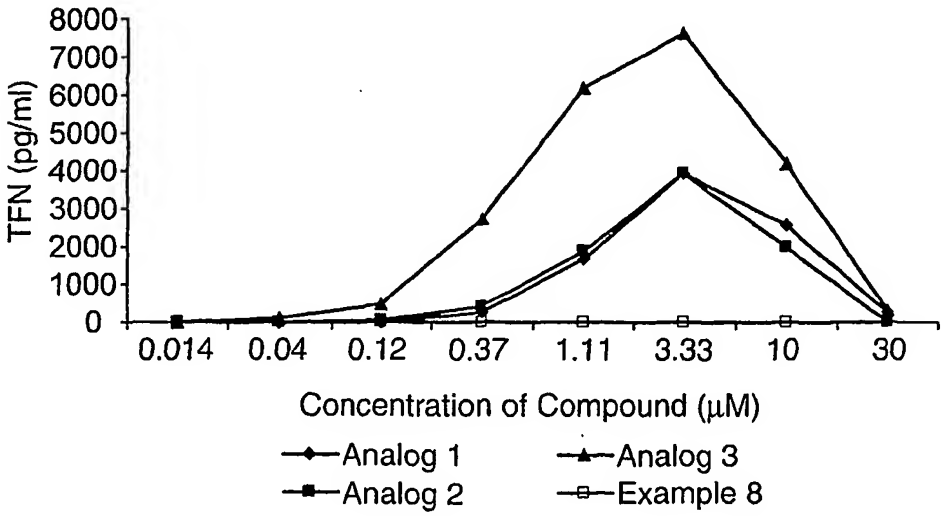
(54) Title: HYDROXYALKYL SUBSTITUTED IMIDAZOQUINOLINE COMPOUNDS AND METHODS



(57) Abstract: Certain imidazoquinolines with a hydroxymethyl or hydroxyethyl substituent at the 2-position, and an aryl or heteroaryl substituent at the 7-position, pharmaceutical compositions containing the compounds, intermediates, methods of making and methods of use of these compounds as immunomodulators, for preferentially inducing IFN-α biosynthesis in animals and in the treatment of diseases including viral and neoplastic diseases are disclosed.

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Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

HYDROXYALKYL SUBSTITUTED IMIDAZOQUINOLINE COMPOUNDS AND METHODS

CROSS REFERENCE TO RELATED APPLICATIONS

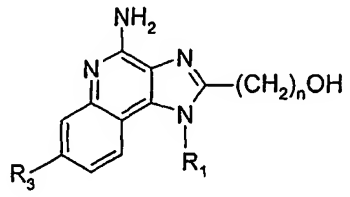
The present invention claims priority to U.S. Provisional Application Serial No. 60/655495, filed February 23, 2005, which is incorporated herein by reference.

BACKGROUND

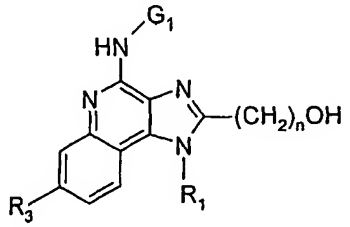
Certain compounds have been found to be useful as immune response modifiers (IRMs), rendering them useful in the treatment of a variety of disorders. However, there continues to be interest in and a need for compounds that have the ability to modulate the immune response, by induction of cytokine biosynthesis or other means.

SUMMARY

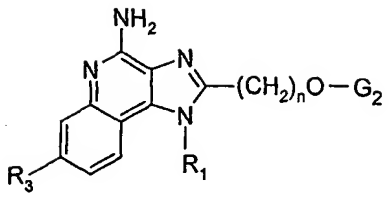
The present invention provides a new class of compounds which preferentially induce the biosynthesis of interferon (α) (IFN-α) in animals. Such compounds are of the following Formulas I, II, and III:



I



II



III

wherein R_1, R_3, G_1, G_2, and n are as defined below.

It has now surprisingly been discovered that the amount of TNF-α induced by the 2-(hydroxyalkyl) substituted compounds of the invention is substantially less than the amount of TNF-α induced by closely related analogs having an alkyl or alkyl ether substituent at the 2-position and that the compounds of the invention still retain the ability to induce the biosynthesis of IFN-α. See, for example, Figures 1 and 2 below. The reduction in the amount of TNF-α induced is seen over a broad range of test concentrations. In some embodiments the amount of TNF-α induced by the compounds of the invention is at least two-fold less than the amount of TNF-α induced by analogs having an alkyl or alkyl ether substituent at the 2-position. In other embodiments the amount of TNF-α induced by the compounds of the invention is at least three-fold less than the amount of TNF-α induced by analogs having an alkyl or alkyl ether substituent at the 2-position. In still other embodiments the amount of TNF-α induced by the compounds of the invention is at least four-fold less than the amount of TNF-α induced by analogs having an alkyl or alkyl ether substituent at the 2-position.

As used herein "substantially less than the amount of TNF-α " means that there is at least a two-fold reduction in the maximal TNF-α response as determined using the test methods described herein.

The compounds or salts of Formulas I, II, and III are especially useful as immune response modifiers due to their ability to preferentially induce interferon-α, thus providing a benefit over compounds that also induce pro-inflammatory cytokines (e.g. TNF-α) or that induce pro-inflammatory cytokines at higher levels.

A compound is said to preferentially induce IFN-α if, when tested according to the test methods described herein, the effective minimum concentration for IFN-α induction is less than the effective minimum concentration for TNF-α induction. In some embodiments, the effective minimum concentration for IFN-α induction is at least 3-fold less than the effective minimum concentration for TNF-α induction. In some

embodiments, the effective minimum concentration for IFN-α induction is at least 6-fold less than the effective minimum concentration for TNF-α induction. In other embodiments, the effective minimum concentration for IFN-α induction is at least 9-fold less than the effective minimum concentration for TNF-α induction. In some embodiments, when tested according to the test methods described herein, the amount TNF-α induced by compounds of the invention is at or below the background level of TNF-α in the test method.

The invention further provides pharmaceutical compositions containing an effective amount of a compound or salt of Formulas I, II, and/or III and methods of preferentially inducing the biosynthesis of IFN-α in an animal, and treating a viral infection or disease and/or treating a neoplastic disease in an animal by administering an effective amount of a compound or salt of Formulas I, II, and/or III or a pharmaceutical compositions containing an effective amount of a compound or salt of Formulas I, II, and/or III to the animal.

In addition, methods of synthesizing compounds of Formulas I, II, and III and intermediates useful in the synthesis of these compounds are provided.

As used herein, "a," "an," "the," "at least one," and "one or more" are used interchangeably.

The terms "comprises" and variations thereof do not have a limiting meaning where these terms appear in the description and claims.

The above summary of the present invention is not intended to describe each disclosed embodiment or every implementation of the present invention. The description that follows more particularly exemplifies illustrative embodiments. In several places throughout the description, guidance is provided through lists of examples, which examples can be used in various combinations. In each instance, the recited list serves only as a representative group and should not be interpreted as an exclusive list.

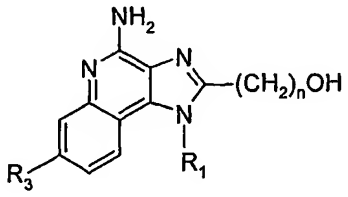
BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the IFN-α dose response curves (corresponding to values shown in Table 3 below) for Example 8, Analog 1, Analog 2, and Analog 3.

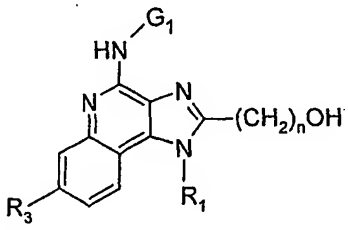
Figure 2 shows the TNF-α dose response curves (corresponding to values shown in Table 3 below) for Example 8, Analog 1, Analog 2, and Analog 3.

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS OF THE INVENTION

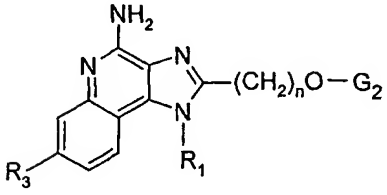
The present invention provides compounds of the following Formulas I, II, and III:



I



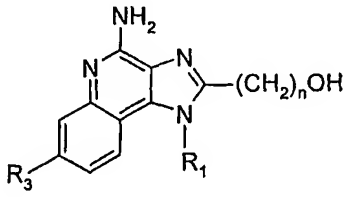
II



III

wherein R_1, R_3, G_1, G_2, and n are as defined below; and pharmaceutically acceptable salts thereof.

In one embodiment, the present invention provides a compound of the following Formula I:



I

wherein:

n is 1 or 2;

R_1 is selected from the group consisting of:

-R_4,

-X-R_4,

-X-Y-R_4, and

-X-R_5;

R_3 is selected from the group consisting of:

-Z-Ar,

-Z-Ar'-Y-R_4, and

-Z-Ar'-X-Y-R_4;

Ar is selected from the group consisting of aryl and heteroaryl both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, amino, alkylamino, and dialkylamino;

Ar' is selected from the group consisting of arylene and heteroarylene both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, amino, alkylamino, and dialkylamino;

X is alkylene optionally interrupted by one -O- group;

Y is selected from the group consisting of:

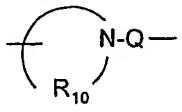
-O-,

-C(R_6)-,

-C(R_6)-N(R_8)-,

-S(O)$_{0-2}$-,

-N(R_8)-Q-,



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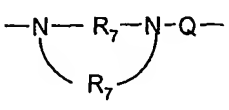

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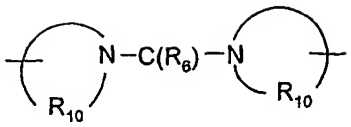
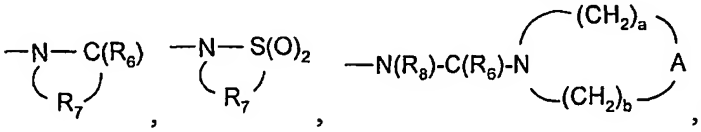

;

Z is selected from the group consisting of a bond and alkylene;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, and heterocyclyl, wherein the alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclyl, amino, alkylamino, dialkylamino, and, in the case of alkyl, alkenyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of: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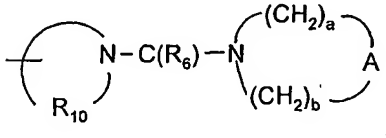

;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R_{10} is C_{3-8} alkylene;

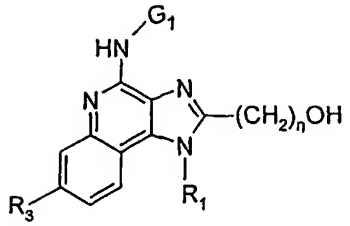
A is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(Q-R_4)-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-S-$; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention provides a compound of the following Formula II, which is a prodrug:



II

wherein:

G_1 is selected from the group consisting of:

-C(O)-R',

α-aminoacyl,

α-aminoacyl-α-aminoacyl,

-C(O)-O-R',

-C(O)-N(R")R',

-C(=NY')-R',

-CH(OH)-C(O)-OY',

-CH(OC_{1-4} alkyl)Y_0,

-CH_2Y_1, and

-$CH(CH_3)Y_1$;

R' and R" are independently selected from the group consisting of C_{1-10} alkyl, C_{3-7} cycloalkyl, phenyl, benzyl, and 2-phenylethyl, each of which may be unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, hydroxy, nitro, cyano, carboxy, C_{1-6} alkyl, C_{1-4} alkoxy, aryl, heteroaryl, aryl-C_{1-4} alkylenyl, heteroaryl-C_{1-4} alkylenyl, halo-C_{1-4} alkylenyl, halo-C_{1-4} alkoxy, -O-C(O)-CH_3, -C(O)-O-CH_3, -C(O)-NH_2, -O-CH_2-C(O)-NH_2, -NH_2, and –$S(O)_2$-NH_2, with the proviso that R" can also be hydrogen;

α-aminoacyl is an α-aminoacyl group derived from an α-amino acid selected from the group consisting of racemic, D-, and L-amino acids;

Y' is selected from the group consisting of hydrogen, C_{1-6} alkyl, and benzyl;

Y_0 is selected from the group consisting of C_{1-6} alkyl, carboxy-C_{1-6} alkylenyl, amino-C_{1-4} alkylenyl, mono-*N*-C_{1-6} alkylamino-C_{1-4} alkylenyl, and di-*N,N*-C_{1-6} alkylamino-C_{1-4} alkylenyl;

Y_1 is selected from the group consisting of mono-*N*-C_{1-6} alkylamino,

di-*N,N*-C_{1-6} alkylamino, morpholin-4-yl, piperidin-1-yl, pyrrolidin-1-yl, and 4-C_{1-4} alkylpiperazin-1-yl;

n is 1 or 2;

R_1 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$, and

$-X-R_5$;

R_3 is selected from the group consisting of:

-Z-Ar,

$-Z-Ar'-Y-R_4$, and

$-Z-Ar'-X-Y-R_4$;

Ar is selected from the group consisting of aryl and heteroaryl both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, amino, alkylamino, and dialkylamino;

Ar' is selected from the group consisting of arylene and heteroarylene both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, amino, alkylamino, and dialkylamino;

X is alkylene optionally interrupted by one -O- group;

Y is selected from the group consisting of:

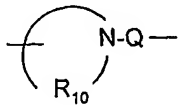
-O-,

$-C(R_6)-$,

$-C(R_6)-N(R_8)-$,

$-S(O)_{0-2}-$,

$-N(R_8)-Q-$,



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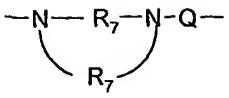

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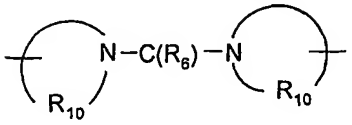
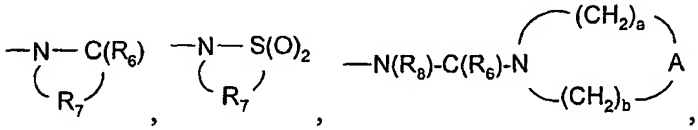


;

Z is selected from the group consisting of a bond and alkylene;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, and heterocyclyl, wherein the alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclyl, amino, alkylamino, dialkylamino, and, in the case of alkyl, alkenyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



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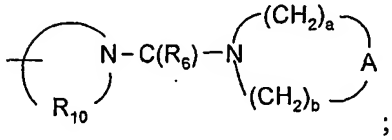


;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R_{10} is C_{3-8} alkylene;

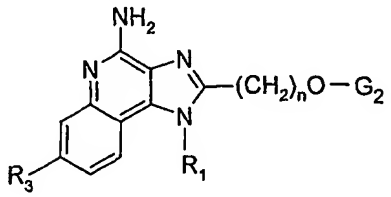
A is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and -N(Q-R_4)-;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-S-$; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention provides a compound of the following Formula III, which is a prodrug:



III

wherein:

G_2 is selected from the group consisting of:

$-X_2-C(O)-R'$,

α-aminoacyl,

α-aminoacyl-α-aminoacyl,

$-X_2-C(O)-O-R'$, and

$-C(O)-N(R'')R'$;

X_2 is selected from the group consisting of a bond; $-CH_2-O-$; $-CH(CH_3)-O-$; $-C(CH_3)_2-O-$; and, in the case of $-X_2-C(O)-O-R'$, $-CH_2-NH-$;

R' and R" are independently selected from the group consisting of C_{1-10} alkyl, C_{3-7} cycloalkyl, phenyl, benzyl, and 2-phenylethyl, each of which may be unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, hydroxy, nitro, cyano, carboxy, C_{1-6} alkyl, C_{1-4} alkoxy, aryl, heteroaryl, aryl-C_{1-4} alkylenyl, heteroaryl-C_{1-4} alkylenyl, halo-C_{1-4} alkylenyl, halo-C_{1-4} alkoxy, $-O-C(O)-CH_3$, $-C(O)-O-CH_3$, $-C(O)-NH_2$, $-O-CH_2-C(O)-NH_2$, $-NH_2$, and $-S(O)_2-NH_2$, with the proviso that R" can also be hydrogen;

α-aminoacyl is an α-aminoacyl group derived from an α-amino acid selected from the group consisting of racemic, D-, and L-amino acids;

n is 1 or 2;

R_1 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$, and

$-X-R_5$;

R_3 is selected from the group consisting of:

-Z-Ar,

-Z-Ar'-Y-R_4, and

-Z-Ar'-X-Y-R_4;

Ar is selected from the group consisting of aryl and heteroaryl both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, amino, alkylamino, and dialkylamino;

Ar' is selected from the group consisting of arylene and heteroarylene both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, amino, alkylamino, and dialkylamino;

X is alkylene optionally interrupted by one -O- group;

Y is selected from the group consisting of:

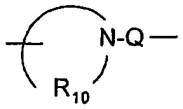
-O-,

-$C(R_6)$-,

-$C(R_6)$-$N(R_8)$-,

-$S(O)_{0-2}$-,

-$N(R_8)$-Q-,



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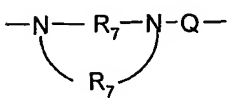
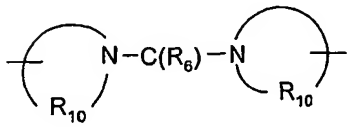


, and



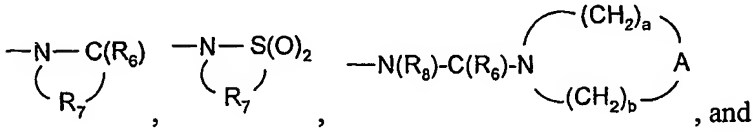
;

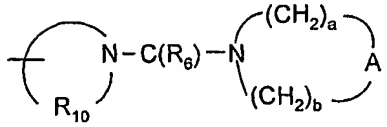
Z is selected from the group consisting of a bond and alkylene;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, and heterocyclyl, wherein the alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, and heterocyclyl groups can be

unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclyl, amino, alkylamino, dialkylamino, and, in the case of alkyl, alkenyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:


, and


;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(Q-R_4)-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-S-$; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7; or a pharmaceutically acceptable salt thereof.

As used herein, the terms "alkyl", "alkenyl", "alkynyl" and the prefix "alk-" are inclusive of both straight chain and branched chain groups and of cyclic groups, e.g., cycloalkyl and cycloalkenyl. Unless otherwise specified, these groups contain from 1 to 20 carbon atoms, with alkenyl groups containing from 2 to 20 carbon atoms, and alkynyl groups containing from 2 to 20 carbon atoms. In some embodiments, these groups have a total of up to 10 carbon atoms, up to 8 carbon atoms, up to 6 carbon atoms, or up to 4 carbon atoms. Cyclic groups can be monocyclic or polycyclic and preferably have from 3 to 10 ring carbon atoms. Exemplary cyclic groups include cyclopropyl, cyclopropylmethyl, cyclobutyl, cyclobutylmethyl, cyclopentyl, cyclopentylmethyl,

cyclohexyl, cyclohexylmethyl, adamantyl, and substituted and unsubstituted bornyl, norbornyl, and norbornenyl.

Unless otherwise specified, "alkylene", "alkenylene", and "alkynylene" are the divalent forms of the "alkyl", "alkenyl", and "alkynyl" groups defined above. The terms, "alkylenyl", "alkenylenyl", and "alkynylenyl" are use when "alkylene", "alkenylene", and "alkynylene", respectively, are substituted. For example, an arylalkylenyl group comprises an alkylene moiety to which an aryl group is attached.

The term "haloalkyl" is inclusive of groups that are substituted by one or more halogen atoms, including perfluorinated groups. This is also true of other groups that include the prefix "halo-." Examples of suitable haloalkyl groups are chloromethyl, trifluoromethyl, and the like.

The term "aryl" as used herein includes carbocyclic aromatic rings or ring systems. Examples of aryl groups include phenyl, naphthyl, biphenyl, fluorenyl and indenyl.

Unless otherwise indicated, the term "heteroatom" refers to the atoms O, S, or N.

The term "heteroaryl" includes aromatic rings or ring systems that contain at least one ring heteroatom (e.g., O, S, N). In some embodiments, the term "heteroaryl" includes a ring or ring system that contains 2-12 carbon atoms, 1-3 rings, 1-4 heteroatoms, and O, S, and N as the heteroatoms. Exemplary heteroaryl groups include furyl, thienyl, pyridyl, quinolinyl, isoquinolinyl, indolyl, isoindolyl, triazolyl, pyrrolyl, tetrazolyl, imidazolyl, pyrazolyl, oxazolyl, thiazolyl, benzofuranyl, benzothiophenyl, carbazolyl, benzoxazolyl, pyrimidinyl, benzimidazolyl, quinoxalinyl, benzothiazolyl, naphthyridinyl, isoxazolyl, isothiazolyl, purinyl, quinazolinyl, pyrazinyl, 1-oxidopyridyl, pyridazinyl, triazinyl, tetrazinyl, oxadiazolyl, thiadiazolyl, and so on.

The term "heterocyclyl" includes non-aromatic rings or ring systems that contain at least one ring heteroatom (e.g., O, S, N) and includes all of the fully saturated and partially unsaturated derivatives of the above mentioned heteroaryl groups. In some embodiments, the term "heterocyclyl" includes a ring or ring system that contains 2-12 carbon atoms, 1-3 rings, 1-4 heteroatoms, and O, S, and N as the heteroatoms. Exemplary heterocyclyl groups include pyrrolidinyl, tetrahydrofuranyl, morpholinyl, thiomorpholinyl, 1,1-dioxothiomorpholinyl, piperidinyl, piperazinyl, thiazolidinyl, imidazolidinyl, isothiazolidinyl, tetrahydropyranyl, quinuclidinyl, homopiperidinyl (azepanyl), 1,4-oxazepanyl, homopiperazinyl (diazepanyl), 1,3-dioxolanyl, aziridinyl, azetidinyl,

dihydroisoquinolin-(1*H*)-yl, octahydroisoquinolin-(1*H*)-yl, dihydroquinolin-(2*H*)-yl, octahydroquinolin-(2*H*)-yl, dihydro-1*H*-imidazolyl, 3-azabicyclo[3.2.2]non-3-yl, and the like.

The term "heterocyclyl" includes bicylic and tricyclic heterocyclic ring systems. Such ring systems include fused and/or bridged rings and spiro rings. Fused rings can include, in addition to a saturated or partially saturated ring, an aromatic ring, for example, a benzene ring. Spiro rings include two rings joined by one spiro atom and three rings joined by two spiro atoms.

When "heterocyclyl" contains a nitrogen atom, the point of attachment of the heterocyclyl group may be the nitrogen atom.

The terms "arylene", "heteroarylene", and "heterocyclylene" are the divalent forms of the "aryl", "heteroaryl", and "heterocyclyl" groups defined above. The terms, "arylenyl", "heteroarylenyl", and "heterocyclylenyl" are used when "arylene," "heteroarylene," and "heterocyclylene", respectively, are substituted. For example, an alkylarylenyl group comprises an arylene moiety to which an alkyl group is attached.

When a group (or substituent or variable) is present more than once in any Formula described herein, each group (or substituent or variable) is independently selected, whether explicitly stated or not. For example, for the formula -N(R_8)-C(O)-N(R_8)- each R_8 group is independently selected. In another example, when R_1 and R_3 each contain an R_4 group then each R_4 group is independently selected. In a further example, when two Y groups are present and each Y group contains one or more R_8 groups, then each Y group and each R_8 group is independently selected.

The invention is inclusive of the compounds described herein in any of their pharmaceutically acceptable forms, including isomers (e.g., diastereomers and enantiomers), salts, solvates, polymorphs, and the like. In particular, if a compound is optically active, the invention specifically includes each of the compound's enantiomers as well as racemic mixtures of the enantiomers. It should be understood that the term "compound" includes any or all of such forms, whether explicitly stated or not (although at times, "salts" are explicitly stated).

The term "prodrug" means a compound that can be transformed in vivo to yield an immune response modifying compound including any of the salt, solvated, polymorphic, or isomeric forms described above. The prodrug, itself, may be an immune response

modifying compound including any of the salt, solvated, polymorphic, or isomeric forms described above. The transformation may occur by various mechanisms, such as through a chemical (e.g., solvolysis or hydrolysis, for example, in the blood) or enzymatic biotransformation. A discussion of the use of prodrugs is provided by T. Higuchi and W. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A. C. S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

For any of the compounds presented herein, each one of the following variables (e.g., Y, X, Z, R_1, R_3, Q, G_1, G_2, n, and so on) in any of its embodiments can be combined with any one or more of the other variables in any of their embodiments and associated with any one of the formulas described herein, as would be understood by one of skill in the art. Each of the resulting combinations of variables is an embodiment of the present invention.

For certain embodiments of Formula I, II, or III, n is 1.

For certain embodiments of Formula I, II, or III, n is 2.

For certain embodiments of Formula I, II, or III, including any one of the above embodiments, R_1 is selected from the group consisting of alkyl, aminoalkyl, dihydroxyalkyl, haloalkyl, and hydroxyalkyl. For certain of these embodiments, R_1 is selected from the group consisting of methyl, ethyl, n-propyl, n-butyl, 2-methylpropyl, 2-amino-2-methylpropyl, 3-amino-2,2-dimethylpropyl, 2,3-dihydroxypropyl, 2-fluoro-2-methylpropyl, and 2-hydroxy-2-methylpropyl. Alternatively, for certain of these embodiments, R_1 is selected from the group consisting of (1-hydroxycyclobutyl)methyl, (1-hydroxycyclopentyl)methyl, and (1-hydroxycyclohexyl)methyl.

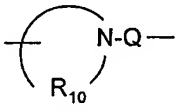
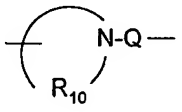
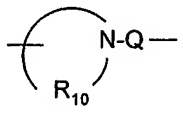
For certain embodiments of Formula I, II, or III, including any one of the above embodiments, R_1 is heterocyclylalkylenyl wherein heterocyclyl is unsubstituted or substituted by one or more substituents independently selected from the group consisting of C_{1-4} alkyl, hydroxy, and oxo, except where R_1 as defined does not include this definition. For certain of these embodiments, R_1 is other than 3-(2-oxopyrrolidin-1-yl)propyl when R_3 is phenyl or pyridin-4-yl. For certain of these embodiments, heterocyclyl is selected from the group consisting of 1,3-dioxolanyl, tetrahydropyranyl, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, and morpholinyl, and alkylenyl is

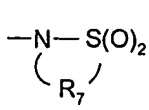
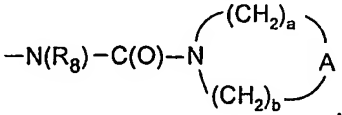
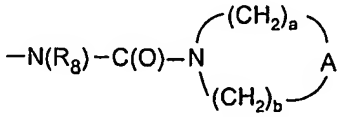
C_{1-4} alkylenyl. For certain of these embodiments, heterocyclyl is selected from the group consisting of 1,3-dioxolanyl, tetrahydropyranyl, tetrahydrofuranyl, piperidinyl, and morpholinyl, and alkylenyl is C_{1-4} alkylenyl. For certain of these embodiments, as well as any one of the above embodiments, R_1 is selected from the group consisting of tetrahydro-2*H*-pyran-4-ylmethyl and (2,2-dimethyl-1,3-dioxolan-4-yl)methyl, except where R_1 as defined does not include this definition. Alternatively, for certain of these embodiments, R_1 is (4-hydroxytetrahydro-2*H*-pyran-4-yl)methyl.

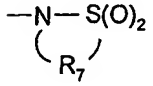
For certain embodiments of Formula I, II, or III, R_1 is other than 3-(2-oxopyrrolidin-1-yl)propyl when R_3 is phenyl or pyridin-4-yl.

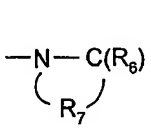
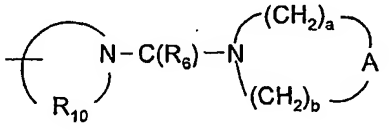
For certain embodiments of Formula I, II, or III, including any one of the above embodiments, R_1 is -X-Y-R_4, except where R_1 as defined does not include this definition, wherein X is C_{1-6} alkylene which may be interrupted by one -O- group; Y is selected from the group consisting of -N(R_8)-C(O)-, -N(R_8)-S(O)$_2$-, -N(R_8)-C(O)-N(R_8)-, and -S(O)$_2$- wherein R_8 is selected from hydrogen and methyl; and R_4 is selected from the group consisting of C_{1-6} alkyl, isoquinolinyl, *N*-methylimidazolyl, pyridinyl, quinolinyl, phenyl, and phenyl substituted by a substituent selected from the group consisting of chloro, cyano, fluoro, hydroxy, and methyl. For certain of these embodiments, as well as any one of the above embodiments, R_1 is selected from the group consisting of 2-[(cyclopropylcarbonyl)amino]ethyl, 4-[(cyclopropylcarbonyl)amino]butyl, 2-[(cyclohexylcarbonyl)amino]-2-methylpropyl, 2-{[(1-methylethyl)carbonyl]amino}ethyl, 4-{[(1-methylethyl)carbonyl]amino}butyl, 2-methyl-2-{[(1-methylethyl)carbonyl]amino}propyl, 2-[(methylsulfonyl)amino]ethyl, 4-[(methylsulfonyl)amino]butyl, 2-methyl-2-[(methylsulfonyl)amino]propyl, 2-methyl-2-({[(1-methylethyl)amino]carbonyl}amino)propyl, 2-methyl-2-[2-(methylsulfonyl)ethoxy]propyl, and 2,2-dimethyl-3-(methylsulfonyl)propyl, except where R_1 as defined does not include this definition. Alternatively, for certain of these embodiments, R_1 is selected from the group consisting of 4-(propylaminocarbonylamino)butyl, 4-(propylcarbonylamino)butyl, 4-(cyclopentylaminocarbonylamino)butyl, and 4-(cyclopentylcarbonylamino)butyl.

For certain embodiments of Formula I, II, or III, including any one of the above embodiments, R_1 is -X-Y-R_4, except where R_1 as defined does not include this definition,

wherein X is C_{1-6} alkylene which may be interrupted by an -O- group; Y is selected from the group consisting of $-N(R_8)-C(O)-$, $-N(R_8)-S(O)_2-$, $-N(R_8)-C(O)-N(R_8)-$, $-N(R_8)-S(O)_2-N(R_8)-$, $-S(O)_2-$, and  wherein Q is -C(O)-, -C(O)-NH-, or $S(O)_2-$, R_{10} is pentylene, R_8 is hydrogen or methyl; and R_4 is selected from the group consisting of C_{1-6} alkyl, hydroxyC_{1-6} alkyl, isoquinolinyl, *N*-methylimidazolyl, pyridinyl, quinolinyl, benzyl, 1-phenylethyl, phenyl, and phenyl substituted by a substituent selected from the group consisting of chloro, cyano, fluoro, hydroxy, and methyl. For certain of these embodiments, X is C_{1-6} alkylene, Y is selected from the group consisting of $-N(R_8)-C(O)-$, $-N(R_8)-S(O)_2-$, and $-N(R_8)-C(O)-N(R_8)-$, and R_4 is selected from the group consisting of C_{1-4} alkyl, hydroxyC_{1-4} alkyl, pyridinyl, benzyl, 1-phenylethyl, phenyl, and phenyl substituted by a substituent selected from the group consisting of chloro, cyano, fluoro, hydroxy, and methyl. Alternatively, for certain of these embodiments, X is C_{1-6} alkylene, Y is  wherein Q is -C(O)-, -C(O)-NH-, or $S(O)_2-$, and R_{10} is pentylene, and R_4 is C_{1-4} alkyl. For certain of these embodiments where Y is  , X is methylene. Alternatively, for certain of these embodiments, Y is $-NH-S(O)_2-N(R_8)-$, R_8 is methyl, and R_4 is C_{1-4} alkyl. For certain of these embodiments where Y is $-NH-S(O)_2-N(R_8)-$, X is C_{2-6} alkylene.

For certain embodiments of Formula I, II, or III, including any one of the above embodiments, R_1 is $-X-R_5$, except where R_1 as defined does not include this definition, wherein X is C_{1-6} alkylene, and R_5 is  or  . For certain of these embodiments, R_5 is  wherein R_8 is hydrogen, A is -O-, $-CH_2-$, or $-N(Q-R_4)-$, and a and b are each 2. For certain of these embodiments,

Q-R_4 is methyl. Alternatively, for certain of these embodiments, R_5 is  . For certain of these embodiments, as well as any one of the above embodiments, R_1 is selected from the group consisting of 4-(1,1-dioxidoisothiazolidin-2-yl)butyl, 4-[(4-morpholinecarbonyl)amino]butyl, and 2-[(4-morpholinecarbonyl)amino]ethyl, except where R_1 as defined does not include this definition.

For certain embodiments of Formula I, II, or III, including any one of the above embodiments, R_1 is -X-R_5, except where R_1 as defined does not include this definition, wherein X is C_{1-4} alkylene, and R_5 is  or  wherein R_6 is =O, R_7 is propylene, R_{10} is pentylene, A is -O-, and a and b are each 2. For certain of these embodiments, R_1 is other than 3-(2-oxopyrrolidin-1-yl)propyl when R_3 is phenyl or pyridin-4-yl.

For certain embodiments of Formula I, II, or III, including any one of the above embodiments, Z is a bond.

For certain embodiments of Formula I, II, or III, including any one of the above embodiments, R_3 is phenyl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, or quinolin-3-yl any of which may be unsubstituted or substituted by one or more substituents selected from the group consisting of alkyl, alkoxy, halogen, hydroxy, and hydroxyalkyl. For certain of these embodiments, when phenyl is substituted by alkyl, alkyl is at the 3-position of the phenyl group. For certain of these embodiments, R_3 is selected from the group consisting of pyridin-3-yl, pyridin-4-yl, 6-fluoropyridin-3-yl, 5-(hydroxymethyl)pyridin-3-yl, 2-ethoxyphenyl, and quinolin-3-yl.

For certain embodiments of Formula I, II, or III, including any one of the above embodiments, R_3 is thien-3-yl, phenyl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, or quinolin-3-yl any of which may be unsubstituted or substituted by one or more substituents selected from the group consisting of alkyl, alkoxy, halogen, cyano, hydroxy, and hydroxyalkyl, except where R_3 as defined does not include this definition. For certain of these embodiments, when phenyl is substituted by alkyl, alkyl is at the 3-position of the phenyl group.

For certain embodiments of Formula I, II, or III, including any one of the above embodiments, R_3 is -Ar'-Y-R_4, except where R_3 as defined does not include this definition, wherein Ar' is phenylene, Y is selected from the group consisting of -C(O)-, -C(O)-N(R_8)-, -N(R_8)-C(O)-, -N(R_8)-S(O)$_2$-, and -N(R_8)-C(O)-N(R_8)- wherein R_8 is selected from hydrogen and methyl; and R_4 is selected from the group consisting of C_{1-6} alkyl, morpholin-4-yl, phenyl, and phenyl substituted by a substituent selected from the group consisting of alkyl, alkoxy, halogen, hydroxy, and hydroxyalkyl.

For certain embodiments of Formula I, II, or III, including any one of the above embodiments, except where R_3 as defined does not include this definition, R_3 is -Ar'-Y-R_4, wherein Ar' is phenylene, Y is selected from the group consisting of -C(O)-, -C(O)-N(R_8)-, -N(R_8)-C(O)-, -N(R_8)-S(O)$_2$-, and -N(R_8)-C(O)-N(R_8)- wherein R_8 is selected from hydrogen and methyl; and R_4 is selected from the group consisting of C_{1-6} alkyl, phenyl, and phenyl substituted by a substituent selected from the group consisting of alkyl, alkoxy, halogen, hydroxy, and hydroxyalkyl; with the proviso that when Y is -C(O)-N(R_8)- or -N(R_8)-C(O)-N(R_8)- then R_4 can also be hydrogen; and with the further proviso that when Y is -C(O)- or -N(R_8)-C(O)- then R_4 can also be morpholin-4-yl, piperidin-1-yl, or pyrrolidin-1-yl. For certain of these embodiments, Y is -C(O)-NH-, and R_4 is hydrogen or C_{1-4} alkyl. For certain of these embodiments, R_4 is hydrogen. Alternatively, for certain of these embodiments, Y is -NH-C(O)-, and R_4 is C_{1-4} alkyl. Alternatively, for certain of these embodiments, Y is -C(O)-, and R_4 is morpholin-4-yl, piperidin-1-yl, or pyrrolidin-1-yl. For certain of these embodiments, R_3 is 3-(methylsulfonylamino)phenyl, 3-(pyrrolidin-1-ylcarbonyl)phenyl, or 3-(morpholin-4-ylcarbonyl)phenyl.

For certain embodiments, for example, embodiments of Formula I, the present invention provides a compound selected from the group consisting of 2-hydroxymethyl-1-(2-methylpropyl)-7-phenyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine, 2-(2-hydroxyethyl)-1-(2-methylpropyl)-7-phenyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine, 1-(4-amino-2-hydroxymethyl-7-phenyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2-methylpropan-2-ol, and 1-[4-amino-2-(2-hydroxyethyl)-7-phenyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol, or a pharmaceutically acceptable salt thereof.

For certain embodiments, for example, embodiments of Formula I, the present invention provides a compound selected from the group consisting of *N*-[4-(4-amino-2-hydroxymethyl-7-phenyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]methanesulfonamide and

N-{4-[4-amino-2-(2-hydroxyethyl)-7-phenyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl]}methanesulfonamide, or a pharmaceutically acceptable salt thereof.

For certain embodiments, for example, embodiments of Formula I, the present invention provides a compound selected from the group consisting of 2-hydroxymethyl-1-(2-methylpropyl)-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine, 2-(2-hydroxyethyl)-1-(2-methylpropyl)-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine, 1-[4-amino-2-hydroxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol, and 1-[4-amino-2-(2-hydroxyethyl)-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol, or a pharmaceutically acceptable salt thereof.

For certain embodiments, for example, embodiments of Formula I, the present invention provides a compound selected from the group consisting of *N*-{4-[4-amino-2-hydroxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl]}methanesulfonamide and *N*-{4-[4-amino-2-(2-hydroxyethyl)-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl]}methanesulfonamide, or a pharmaceutically acceptable salt thereof.

For certain embodiments, the present invention provides a pharmaceutical composition comprising a therapeutically effective amount of a compound or salt of Formula I, II, III, or of any one of the above embodiments and a pharmaceutically acceptable carrier.

For certain embodiments, the present invention provides a method of preferentially inducing the biosynthesis of IFN-α in an animal comprising administering an effective amount of a compound or salt of Formula I, II, III, or of any one of the above embodiments or the above pharmaceutical composition to the animal.

For certain embodiments, the present invention provides a method of treating a viral disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound or salt of Formula I, II, III, or of any one of the above embodiments or the above pharmaceutical composition to the animal. For certain of these embodiments, the method includes preferentially inducing the biosynthesis of IFN-α.

For certain embodiments, the present invention provides a method of treating a neoplastic disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound or salt of Formula I, II, III, or of any one of the above

embodiments or the above pharmaceutical composition to the animal. For certain of these embodiments, the method includes preferentially inducing the biosynthesis of IFN-α.

For certain embodiments of the above methods, the compound or salt or pharmaceutical composition is administered systemically.

For certain embodiments, R_1 is selected from the group consisting of $-R_4$, $-X-R_4$, $-X-Y-R_4$, and $-X-R_5$.

For certain embodiments, R_1 is $-R_4$.

For certain embodiments, R_1 is selected from the group consisting of alkyl, aminoalkyl, dihydroxyalkyl, haloalkyl, and hydroxyalkyl.

For certain embodiments, R_1 is selected from the group consisting of methyl, ethyl, n-propyl, n-butyl, 2-methylpropyl, 2-amino-2-methylpropyl, 3-amino-2,2-dimethylpropyl, 2,3-dihydroxypropyl, 2-fluoro-2-methylpropyl, and 2-hydroxy-2-methylpropyl.

For certain embodiments, R_1 is selected from the group consisting of (1-hydroxycyclobutyl)methyl, (1-hydroxycyclopentyl)methyl, and (1-hydroxycyclohexyl)methyl.

For certain embodiments, R_1 is heterocyclylalkylenyl wherein heterocyclyl is unsubstituted or substituted by one or more substituents independently selected from the group consisting of C_{1-4} alkyl, hydroxy, and oxo. For certain of these embodiments, R_1 is other than 3-(2-oxopyrrolidin-1-yl)propyl when R_3 is phenyl or pyridin-4-yl.

For certain embodiments, R_1 is heterocyclylalkylenyl wherein heterocyclyl is selected from the group consisting of 1,3-dioxolanyl, tetrahydropyranyl, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, and morpholinyl, and alkylenyl is C_{1-4} alkylenyl.

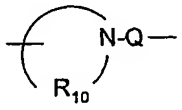
For certain embodiments, R_1 is selected from the group consisting of tetrahydro-2*H*-pyran-4-ylmethyl and (2,2-dimethyl-1,3-dioxolan-4-yl)methyl.

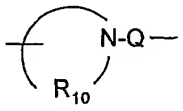
For certain embodiments, R_1 is (4-hydroxytetrahydro-2*H*-pyran-4-yl)methyl.

For certain embodiments, R_1 is $-X-Y-R_4$.

For certain embodiments, R_1 is $-X-Y-R_4$ wherein X is C_{1-6} alkylene which may be interrupted by one -O- group; Y is selected from the group consisting of $-N(R_8)-C(O)-$, $-N(R_8)-S(O)_2-$, $-N(R_8)-C(O)-N(R_8)-$, and $-S(O)_2-$ wherein R_8 is selected from hydrogen and methyl; and R_4 is selected from the group consisting of C_{1-6} alkyl, isoquinolinyl, *N*-methylimidazolyl, pyridinyl, quinolinyl, phenyl, and phenyl substituted by a substituent selected from the group consisting of chloro, cyano, fluoro, hydroxy, and methyl.

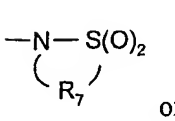
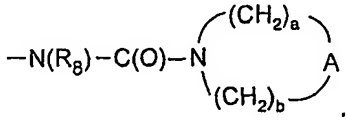
For certain embodiments, R_1 is selected from the group consisting of 2-[(cyclopropylcarbonyl)amino]ethyl, 4-[(cyclopropylcarbonyl)amino]butyl, 2-[(cyclohexylcarbonyl)amino]-2-methylpropyl, 2-{[(1-methylethyl)carbonyl]amino}ethyl, 4-{[(1-methylethyl)carbonyl]amino}butyl, 2-methyl-2-{[(1-methylethyl)carbonyl]amino}propyl, 2-[(methylsulfonyl)amino]ethyl, 4-[(methylsulfonyl)amino]butyl, 2-methyl-2-[(methylsulfonyl)amino]propyl, 2-methyl-2-({[(1-methylethyl)amino]carbonyl}amino)propyl, 2-methyl-2-[2-(methylsulfonyl)ethoxy]propyl, and 2,2-dimethyl-3-(methylsulfonyl)propyl.

For certain embodiments, R_1 is -X-Y-R_4 wherein X is C_{1-6} alkylene which may be interrupted by an -O- group; Y is selected from the group consisting of -N(R_8)-C(O)-, 
-N(R_8)-S(O)$_2$-, -N(R_8)-C(O)-N(R_8)-, -N(R_8)-S(O)$_2$-N(R_8)-, -S(O)$_2$-, and wherein Q is -C(O)-, -C(O)-NH-, or S(O)$_2$-, R_{10} is pentylene, R_8 is hydrogen or methyl; and R_4 is selected from the group consisting of C_{1-6} alkyl, hydroxyC_{1-6} alkyl, isoquinolinyl, *N*-methylimidazolyl, pyridinyl, quinolinyl, benzyl, 1-phenylethyl, phenyl, and phenyl substituted by a substituent selected from the group consisting of chloro, cyano, fluoro, hydroxy, and methyl.

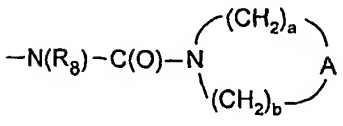
For certain embodiments, R_1 is -X-Y-R_4 wherein X is C_{1-4} alkylene; Y is  ; and R_4 is C_{1-4} alkyl. For certain of these embodiments, R_{10} is pentylene, and Q is selected from the group consisting of -S(O)$_2$-, -C(O)-, and -C(O)-NH-.

For certain embodiments, R_1 is -X-Y-R_4 wherein Y is -NH-S(O)$_2$-N(R_8)-, R_8 is methyl, and R_4 is C_{1-4} alkyl.

For certain embodiments, R_1 is -X-R_5.

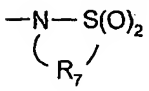
For certain embodiments, R_1 is -X-R_5 wherein X is C_{1-6} alkylene, and R_5 is  or  .

For certain embodiments, R_1 is -X-R_5 wherein X is C_{1-6} alkylene, and R_5 is



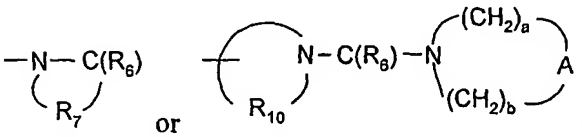
wherein R_8 is hydrogen, A is -O-, -CH_2-, or -N(Q-R_4)-, and a and b are each 2.

For certain embodiments, R_1 is -X-R_5 wherein X is C_{1-6} alkylene, R_5 is



, and R_7 is propylene.

For certain embodiments, R_1 is -X-R_5, wherein X is C_{1-4} alkylene, and R_5 is



wherein R_6 is =O, R_7 is propylene, R_{10} is pentylene, A is -O-, and a and b are each 2. For certain of these embodiments, R_1 is other than 3-(2-oxopyrrolidin-1-yl)propyl when R_3 is phenyl or pyridin-4-yl.

For certain embodiments, R_1 is selected from the group consisting of 4-(1,1-dioxidoisothiazolidin-2-yl)butyl, 4-[(4-morpholinecarbonyl)amino]butyl, and 2-[(4-morpholinecarbonyl)amino]ethyl.

For certain embodiments, R_3 is selected from the group consisting of -Z-Ar, -Z-Ar'-Y-R_4, and -Z-Ar'-X-Y-R_4.

For certain embodiments, R_3 is -Z-Ar.

For certain embodiments, R_3 is thien-3-yl, phenyl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, or quinolin-3-yl any of which may be unsubstituted or substituted by one or more substituents selected from the group consisting of alkyl, alkoxy, halogen, cyano, hydroxy, and hydroxyalkyl. For certain of these embodiments, when phenyl is substituted by alkyl, alkyl is at the 3-position of the phenyl group.

For certain embodiments, R_3 is phenyl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, or quinolin-3-yl any of which may be unsubstituted or substituted by one or more substituents selected from the group consisting of alkyl, alkoxy, halogen, hydroxy, and hydroxyalkyl. For certain of these embodiments, when phenyl is substituted by alkyl, alkyl is at the 3-position of the phenyl group.

For certain embodiments, R_3 is selected from the group consisting of pyridin-3-yl, pyridin-4-yl, 6-fluoropyridin-3-yl, 5-(hydroxymethyl)pyridin-3-yl, 2-ethoxyphenyl, and quinolin-3-yl.

For certain embodiments, R_3 is -Ar'-Y-R_4.

For certain embodiments, R_3 is -Ar'-Y-R_4 wherein Ar' is phenylene, Y is selected from the group consisting of -C(O)-, -C(O)-N(R_8)-, -N(R_8)-C(O)-, -N(R_8)-S(O)$_2$-, and -N(R_8)-C(O)-N(R_8)- wherein R_8 is selected from hydrogen and methyl; and R_4 is selected from the group consisting of C_{1-6} alkyl, phenyl, morpholin-4-yl, and phenyl substituted by a substituent selected from the group consisting of alkyl, alkoxy, halogen, hydroxy, and hydroxyalkyl.

For certain embodiments, R_3 is -Ar'-Y-R_4, wherein Ar' is phenylene, Y is selected from the group consisting of -C(O)-, -C(O)-N(R_8)-, -N(R_8)-C(O)-, -N(R_8)-S(O)$_2$-, and -N(R_8)-C(O)-N(R_8)- wherein R_8 is selected from hydrogen and methyl; and R_4 is selected from the group consisting of C_{1-6} alkyl, phenyl, and phenyl substituted by a substituent selected from the group consisting of alkyl, alkoxy, halogen, hydroxy, and hydroxyalkyl; with the proviso that when Y is -C(O)-N(R_8)- or -N(R_8)-C(O)-N(R_8)- then R_4 can also be hydrogen; and with the further proviso that when Y is -C(O)- or -N(R_8)-C(O)- then R_4 can also be morpholin-4-yl, piperidin-1-yl, or pyrrolidin-1-yl.

For certain embodiments, R_3 is -Ar'-Y-R_4, wherein Ar' is phenylene, Y is -C(O)-NH-, and R_4 is hydrogen or C_{1-4} alkyl.

For certain embodiments, R_3 is -Ar'-Y-R_4, wherein Ar' is phenylene, Y is -NH-C(O)-, and R_4 is C_{1-4} alkyl.

For certain embodiments, R_3 is -Ar'-Y-R_4, wherein Ar' is phenylene, Y is -C(O)-, and R_4 is morpholin-4-yl, piperidin-1-yl, or pyrrolidin-1-yl.

For certain embodiments, R_3 is 3-(methylsulfonylamino)phenyl, 3-(pyrrolidin-1-ylcarbonyl)phenyl, or 3-(morpholin-4-ylcarbonyl)phenyl.

For certain embodiments, R_3 is -Ar'-X-Y-R_4 wherein Ar' is phenylene, X is C_{1-4} alkylene, Y is selected from the group consisting of -N(R_8)-C(O)-, -N(R_8)-S(O)$_2$-, and -N(R_8)-C(O)-N(R_8)- wherein R_8 is selected from hydrogen and methyl; and R_4 is selected from the group consisting of C_{1-6} alkyl, phenyl, and phenyl substituted by a substituent selected from the group consisting of alkyl, alkoxy, halogen, hydroxy, and hydroxyalkyl.

For certain embodiments, R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, and heterocyclyl, wherein the alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclyl, amino, alkylamino, dialkylamino, and, in the case of alkyl, alkenyl, and heterocyclyl, oxo.

For certain embodiments, R_4 is selected from the group consisting of C_{1-6} alkyl, hydroxyC_{1-6} alkyl, isoquinolinyl, *N*-methylimidazolyl, pyridinyl, quinolinyl, benzyl, 1-phenylethyl, phenyl, and phenyl substituted by a substituent selected from the group consisting of chloro, cyano, fluoro, hydroxy, and methyl.

For certain embodiments, R_4 is selected from the group consisting of C_{1-6} alkyl, isoquinolinyl, *N*-methylimidazolyl, pyridinyl, quinolinyl, phenyl, and phenyl substituted by a substituent selected from the group consisting of chloro, cyano, fluoro, hydroxy, and methyl.

For certain embodiments, R_4 is selected from the group consisting of C_{1-6} alkyl, morpholin-4-yl, phenyl, and phenyl substituted by a substituent selected from the group consisting of alkyl, alkoxy, halogen, hydroxy, and hydroxyalkyl.

For certain embodiments, R_4 is selected from the group consisting of C_{1-6} alkyl, phenyl, and phenyl substituted by a substituent selected from the group consisting of alkyl, alkoxy, halogen, hydroxy, and hydroxyalkyl.

For certain embodiments, R_4 is morpholin-4-yl, piperidin-1-yl, or pyrrolidin-1-yl.

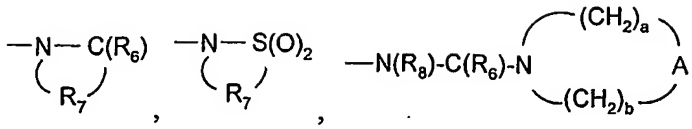
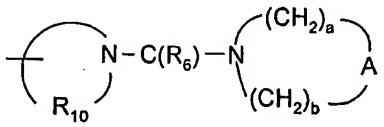
For certain embodiments, R_4 is C_{1-6} alkyl.

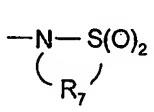
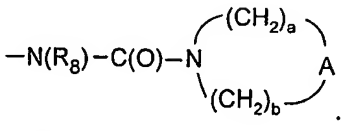
For certain embodiments, R_4 is hydrogen or C_{1-4} alkyl.

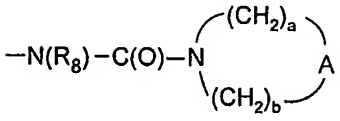
For certain embodiments, R_4 is C_{1-4} alkyl.

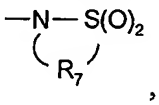
For certain embodiments, R_4 is hydrogen.

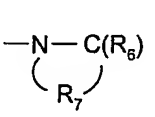
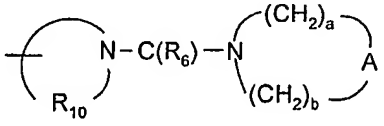
For certain embodiments, R_5 is selected from the group consisting of:


, and

. For certain of these embodiments, -X-R_5 is other than 3-(2-oxopyrrolidin-1-yl)propyl when R_3 is phenyl or pyridin-4-yl.

For certain embodiments, R_5 is  or  .

For certain embodiments, R_5 is  wherein R_8 is hydrogen, A is -O-, $-CH_2-$, or $-N(Q-R_4)-$, and a and b are each 2.

For certain embodiments, R_5 is  , and R_7 is propylene.

For certain embodiments, R_5 is  or  wherein R_6 is =O, R_7 is propylene, R_{10} is pentylene, A is -O-, and a and b are each 2.

For certain embodiments, R_6 is selected from the group consisting of =O and =S.

For certain embodiments, R_6 is =O.

For certain embodiments, R_6 is =S.

For certain embodiments, R_7 is C_{2-7} alkylene.

For certain embodiments, R_7 is C_{2-4} alkylene.

For certain embodiments, R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl.

For certain embodiments, R_8 is selected from the group consisting of hydrogen, C_{1-4} alkyl, and C_{1-4} alkoxyC_{1-4} alkylenyl.

For certain embodiments, R_8 is hydrogen or C_{1-4} alkyl.

For certain embodiments, R_8 is selected from hydrogen and methyl

For certain embodiments, R_8 is methyl.

For certain embodiments, R_8 is hydrogen.

For certain embodiments, R_{10} is C_{3-8} alkylene.

For certain embodiments, R_{10} is C_{4-6} alkylene.

For certain embodiments, R_{10} is pentylene.

For certain embodiments, A is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(Q-R_4)-$.

For certain embodiments, A is -O-, $-CH_2-$, -S-, or $-S(O)_2-$.

For certain embodiments, A is -O-, $-CH_2-$, or $-N(Q-R_4)-$.

For certain embodiments, A is -O- or $-S(O)_2-$.

For certain embodiments, A is -O-.

For certain embodiments, A is $-CH_2-$.

For certain embodiments, A is $-N(Q-R_4)-$.

For certain embodiments, A is $-N(CH_3)-$.

For certain embodiments, Ar is selected from the group consisting of aryl and heteroaryl both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, amino, alkylamino, and dialkylamino.

For certain embodiments, Ar is aryl.

For certain embodiments, Ar is phenyl.

For certain embodiments, Ar is phenyl which may be unsubstituted or substituted by one or more substituents selected from the group consisting of alkyl, alkoxy, halogen, hydroxy, and hydroxyalkyl. For certain of these embodiments, alkyl is at the 3-position of the phenyl group.

For certain embodiments, Ar is heteroaryl.

For certain embodiments, Ar is pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, or quinolin-3-yl any of which may be unsubstituted or substituted by one substituent selected from the group consisting of alkyl, alkoxy, halogen, hydroxy, and hydroxyalkyl.

For certain embodiments, Ar' is selected from the group consisting of arylene and heteroarylene both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy,

haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, amino, alkylamino, and dialkylamino.

For certain embodiments, Ar' is phenylene.

For certain embodiments, Ar' is pyridinylene.

For certain embodiments, including any one of the above embodiments of Formula II, G_1 is selected from the group consisting of -C(O)-R', α-aminoacyl, α-aminoacyl-α-aminoacyl, -C(O)-O-R', -C(O)-N(R")R', -C(=NY')-R', -CH(OH)-C(O)-OY', -CH(OC_{1-4} alkyl)Y_0, -CH_2Y_1, and -$CH(CH_3)Y_1$; R' and R" are independently selected from the group consisting of C_{1-10} alkyl, C_{3-7} cycloalkyl, phenyl, benzyl, and 2-phenylethyl, each of which may be unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, hydroxy, nitro, cyano, carboxy, C_{1-6} alkyl, C_{1-4} alkoxy, aryl, heteroaryl, aryl-C_{1-4} alkylenyl, heteroaryl-C_{1-4} alkylenyl, halo-C_{1-4} alkylenyl, halo-C_{1-4} alkoxy, -O-C(O)-CH_3, -C(O)-O-CH_3, -C(O)-NH_2, -O-CH_2-C(O)-NH_2, -NH_2, and –$S(O)_2$-NH_2, with the proviso that R" can also be hydrogen; α-aminoacyl is an α-aminoacyl group derived from an α-amino acid selected from the group consisting of racemic, D-, and L-amino acids; Y' is selected from the group consisting of hydrogen, C_{1-6} alkyl, and benzyl; Y_0 is selected from the group consisting of C_{1-6} alkyl, carboxy-C_{1-6} alkylenyl, amino-C_{1-4} alkylenyl, mono-*N*-C_{1-6} alkylamino-C_{1-4} alkylenyl, and di-*N,N*-C_{1-6} alkylamino-C_{1-4} alkylenyl; and Y_1 is selected from the group consisting of mono-*N*-C_{1-6} alkylamino, di-*N,N*-C_{1-6} alkylamino, morpholin-4-yl, piperidin-1-yl, pyrrolidin-1-yl, and 4-C_{1-4} alkylpiperazin-1-yl.

For certain embodiments, including any one of the above embodiments of Formula II, G_1 is selected from the group consisting of -C(O)-R', α-aminoacyl, and -C(O)-O-R'. For certain of these embodiments, R' contains one to ten carbon atoms. For certain of these embodiments, α-aminoacyl is an α-C_{2-11} aminoacyl group derived from an α-amino acid selected from the group consisting of racemic, D-, and L-amino acids containing a total of at least 2 carbon atoms and a total of up to 11 carbon atoms, and may also include one or more heteroatoms selected from the group consisting of O, S, and N.

For certain embodiments, including any one of the above embodiments of Formula III, G_2 is selected from the group consisting of -X_2-C(O)-R', α-aminoacyl, α-aminoacyl-α-aminoacyl, -X_2-C(O)-O-R', and -C(O)-N(R")R'. For certain of these embodiments, X_2 is selected from the group consisting of a bond; -CH_2-O-; -$CH(CH_3)$-O-; -$C(CH_3)_2$-O-; and,

in the case of -X_2-C(O)-O-R', -CH_2-NH-; R' and R" are independently selected from the group consisting of C_{1-10} alkyl, C_{3-7} cycloalkyl, phenyl, benzyl, and 2-phenylethyl, each of which may be unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, hydroxy, nitro, cyano, carboxy, C_{1-6} alkyl, C_{1-4} alkoxy, aryl, heteroaryl, aryl-C_{1-4} alkylenyl, heteroaryl-C_{1-4} alkylenyl, halo-C_{1-4} alkylenyl, halo-C_{1-4} alkoxy, -O-C(O)-CH_3, -C(O)-O-CH_3, -C(O)-NH_2, -O-CH_2-C(O)-NH_2, -NH_2, and –$S(O)_2$-NH_2, with the proviso that R" can also be hydrogen; and α-aminoacyl is an α-aminoacyl group derived from an α-amino acid selected from the group consisting of racemic, D-, and L-amino acids.

For certain embodiments, including any one of the above embodiments of Formula III, G_2 is selected from the group consisting of -C(O)-R' and α-aminoacyl, wherein R' is C_{1-6} alkyl or phenyl which is unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, hydroxy, nitro, cyano, carboxy, C_{1-6} alkyl, C_{1-4} alkoxy, aryl, heteroaryl, aryl-C_{1-4} alkylenyl, heteroaryl-C_{1-4} alkylenyl, halo-C_{1-4} alkylenyl, halo-C_{1-4} alkoxy, -O-C(O)-CH_3, -C(O)-O-CH_3, -C(O)-NH_2, -O-CH_2-C(O)-NH_2, -NH_2, and –$S(O)_2$-NH_2.

For certain embodiments, including any one of the above embodiments of Formula III, G_2 is selected from the group consisting of α-amino-C_{2-5} alkanoyl, C_{2-6} alkanoyl, C_{1-6} alkoxycarbonyl, and C_{1-6} alkylcarbamoyl.

For certain embodiments, including any one of the above embodiments which include an α-aminoacyl group, α-aminoacyl is an α-aminoacyl group derived from a naturally occuring α-amino acid selected from the group consisting of racemic, D-, and L-amino acids.

For certain embodiments, including any one of the above embodiments which include an α-aminoacyl group, α-aminoacyl is an α-aminoacyl group derived from an α-amino acid found in proteins, wherein the the amino acid is selected from the group consisting of racemic, D-, and L-amino acids.

For certain embodiments, the hydrogen atom of the hydroxy group of Formula II (including any one of its embodiments) is replaced by G_2, wherein G_2 is defined as in any one of the above embodiments of G_2.

For certain embodiments, Q is selected from the group consisting of a bond, -C(R_6)-, -$S(O)_2$, -C(R_6)-N(R_8)-, -$S(O)_2$-N(R_8)-, -C(R_6)-O-, and -C(R_6)-S-.

For certain embodiments, Q is selected from the group consisting of a bond, $-C(R_6)-$, $-S(O)_2-$, and $-C(R_6)-N(R_8)-$.

For certain embodiments, Q is selected from the group consisting of $-C(O)-$, $-S(O)_2-$, and $-C(O)-N(R_8)-$. In certain of these embodiments, R_8 is hydrogen or methyl.

For certain embodiments, Q is selected from the group consisting of $-S(O)_2-$, $-C(O)-$, and $-C(O)-NH-$.

For certain embodiments, Q is $-C(O)-$.

For certain embodiments, Q is $-S(O)_2-$.

For certain embodiments, Q is $-C(R_6)-N(R_8)-$.

For certain embodiments, Q is $-C(O)-N(R_8)-$ wherein R_8 is hydrogen or methyl.

For certain embodiments, X is alkylene which can be optionally interrupted or terminated by arylene and optionally interrupted by one -O- group.

For certain embodiments, X is C_{1-6} alkylene which may be interrupted by one -O- group.

For certain embodiments, X is C_{1-6} alkylene.

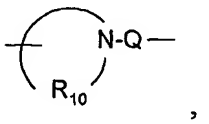
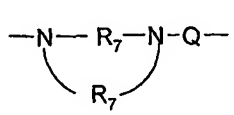
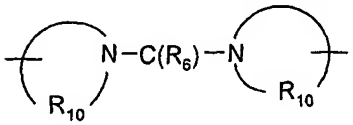
For certain embodiments, X is C_{2-6} alkylene.

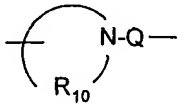
For certain embodiments, X is C_{1-4} alkylene.

For certain embodiments, X is methylene.

For certain embodiments, X is ethylene.

For certain embodiments, X is butylene.

For certain embodiments, Y is selected from the group consisting of -O-,$-C(R_6)-$, $-C(R_6)-N(R_8)-$, $-S(O)_{0-2}-$, $-N(R_8)-Q-$,  ,  , and 

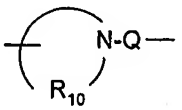
For certain embodiments, Y is selected from the group consisting of $-N(R_8)-C(O)-$, $-N(R_8)-S(O)_2-$, $-N(R_8)-C(O)-N(R_8)-$, $-N(R_8)-S(O)_2-N(R_8)-$, $-S(O)_2-$, and  . In certain of these embodiments, Q is $-C(O)-$, $-C(O)-NH-$, or $S(O)_2-$, R_{10} is pentylene, and R_8 is hydrogen or methyl.

For certain embodiments, Y is selected from the group consisting of -N(R_8)-C(O)-, -N(R_8)-S(O)$_2$-, -N(R_8)-C(O)-N(R_8)-, and -S(O)$_2$-. In certain of these embodiments, R_8 is selected from hydrogen and methyl.

For certain embodiments, Y is selected from the group consisting of -C(O)-, -C(O)-N(R_8)-, -N(R_8)-C(O)-, -N(R_8)-S(O)$_2$-, and -N(R_8)-C(O)-N(R_8)- wherein R_8 is selected from hydrogen and methyl.

For certain embodiments, Y is selected from the group consisting of -N(R_8)-C(O)-, -N(R_8)-S(O)$_2$-, and -N(R_8)-C(O)-N(R_8)- wherein R_8 is selected from hydrogen and methyl.

For certain embodiments, Y is selected from the group consisting of -C(O)-, -N(R_8)-C(O)-, -N(R_8)-S(O)$_2$-, and -N(R_8)-C(O)-N(R_8)-. In certain of these embodiments, R_8 is selected from hydrogen and methyl.

For certain embodiments, Y is 

. For certain of these embodiments, R_{10} is pentylene, and Q is selected from the group consisting of -S(O)$_2$-, -C(O)-, and -C(O)-NH-.

For certain embodiments, Y is -NH-S(O)$_2$-N(R_8)-. In certain of these embodiments, R_8 is methyl.

For certain embodiments, Z is a bond.

For certain embodiments, Z is alkylene.

For certain embodiments, a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7.

For certain embodiments, a and b are each independently 1 to 3.

For certain embodiments, a and b are each 2.

For certain embodiments, a is 1, 2, or 3, and b is 2.

For certain embodiments, n is 1 or 2.

For certain embodiments, n is 1.

For certain embodiments, n is 2.

Preparation of the Compounds

Compounds of the invention may be synthesized by synthetic routes that include processes analogous to those well known in the chemical arts, particularly in light of the

description contained herein. The starting materials are generally available from commercial sources such as Aldrich Chemicals (Milwaukee, Wisconsin, USA) or are readily prepared using methods well known to those skilled in the art (e.g., prepared by methods generally described in Louis F. Fieser and Mary Fieser, *Reagents for Organic Synthesis*, v. 1-19, Wiley, New York, (1967-1999 ed.); Alan R. Katritsky, Otto Meth-Cohn, Charles W. Rees, *Comprehensive Organic Functional Group Transformations*, v. 1-6, Pergamon Press, Oxford, England, (1995); Barry M. Trost and Ian Fleming, *Comprehensive Organic Synthesis*, v. 1-8, Pergamon Press, Oxford, England, (1991); or *Beilsteins Handbuch der organischen Chemie*, 4, Aufl. Ed. Springer-Verlag, Berlin, Germany, including supplements (also available via the Beilstein online database)).

For illustrative purposes, the reaction schemes depicted below provide potential routes for synthesizing the compounds of the present invention as well as key intermediates. For more detailed description of the individual reaction steps, see the EXAMPLES section below. Those skilled in the art will appreciate that other synthetic routes may be used to synthesize the compounds of the invention. Although specific starting materials and reagents are depicted in the reaction schemes and discussed below, other starting materials and reagents can be easily substituted to provide a variety of derivatives and/or reaction conditions. In addition, many of the compounds prepared by the methods described below can be further modified in light of this disclosure using conventional methods well known to those skilled in the art.

In the preparation of compounds of the invention it may sometimes be necessary to protect a particular functionality while reacting other functional groups on an intermediate. The need for such protection will vary depending on the nature of the particular functional group and the conditions of the reaction step. Suitable amino protecting groups include acetyl, trifluoroacetyl, *tert*-butoxycarbonyl (Boc), benzyloxycarbonyl, and 9-fluorenylmethoxycarbonyl (Fmoc). Suitable hydroxy protecting groups include acetyl and silyl groups such as the *tert*-butyl dimethylsilyl group. For a general description of protecting groups and their use, see T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, New York, USA, 1991.

Conventional methods and techniques of separation and purification can be used to isolate compounds of the invention, as well as various intermediates related thereto. Such techniques may include, for example, all types of chromatography (high performance

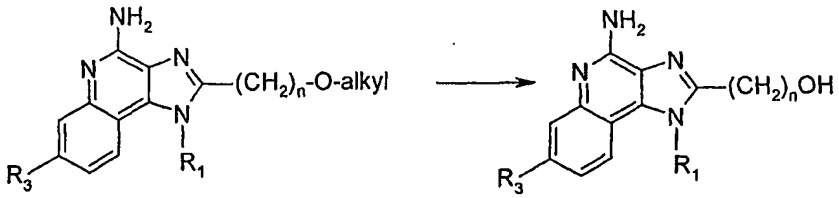
liquid chromatography (HPLC), column chromatography using common absorbents such as silica gel, and thin layer chromatography), recrystallization, and differential (i.e., liquid-liquid) extraction techniques.

In some embodiments, compounds of the invention can be prepared according to Reaction Scheme I, wherein R_1, R_3, and n are as defined above and alkyl is methyl or ethyl.

In Reaction Scheme I an ether substituted 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula X is cleaved to provide a hydroxyalkyl substituted 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula I. The reaction is conveniently carried out by adding a solution of boron tribromide in a suitable solvent such as dichloromethane to a solution or suspension of a compound of Formula X in a suitable solvent such as dichloromethane at ambient or at a sub-ambient temperature, for example, at 0°C. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Numerous compounds of Formula X are known; others can be prepared using known synthetic methods. See United States Patent Application Publication No. 2004/0147543 and the references cited therein.

Reaction Scheme I



X I

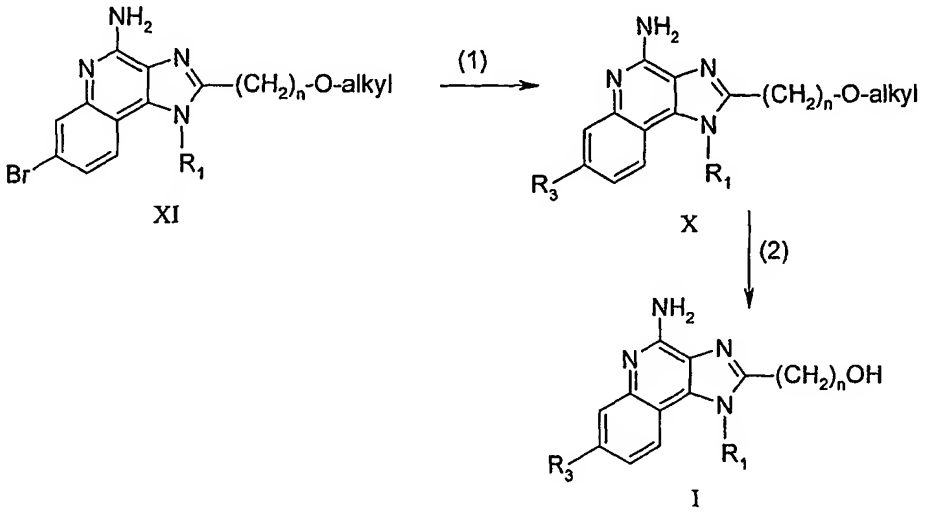
In some embodiments, compounds of the invention can also be prepared according to Reaction Scheme II, wherein R_1, R_3, and n are as defined above and alkyl is methyl or ethyl.

In step (1) of Reaction Scheme II, a 7-bromo 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XI is converted to a 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula X. The reaction can be carried out using known palladium catalyzed coupling reactions such as Suzki coupling, Stille coupling, Sonogashira coupling, and the Heck reaction using the methods described in United States Patent Application Publication No. 2004/0147543.

Numerous compounds of Formula XI are known; others can be prepared using known synthetic methods. See United States Patent Application Publication No. 2004/0147543 and the references cited therein.

In step (2) of Reaction Scheme II, an ether substituted 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula X is cleaved to provide a hydroxyalkyl substituted 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula I using the method described in Reaction Scheme I.

Reaction Scheme II



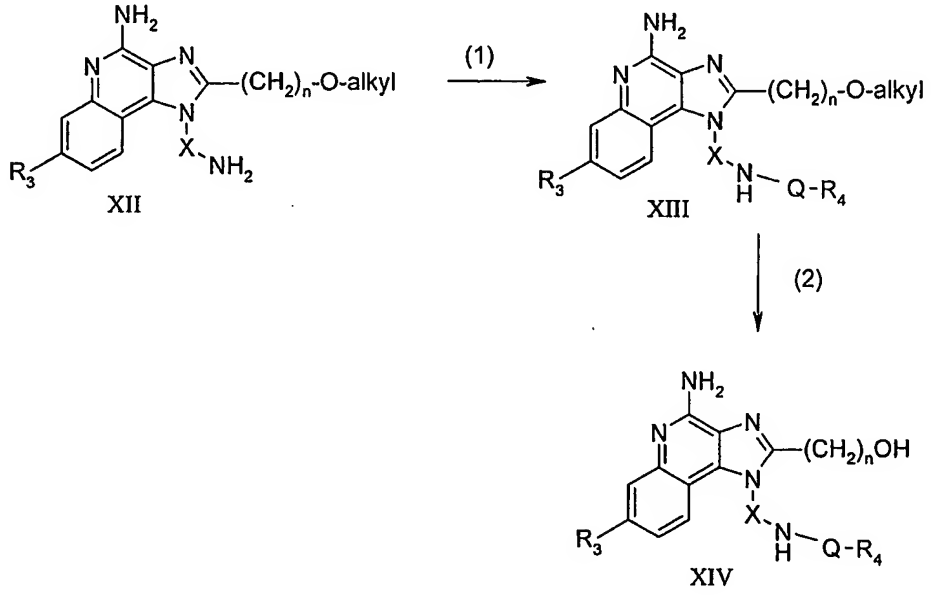
In some embodiments, compounds of the invention can also be prepared according to Reaction Scheme III, wherein R_3, R_4, Q, X, and n are as defined above and alkyl is methyl or ethyl.

In step (1) of Reaction Scheme III, the amino group on the -X-NH_2 substituent of a 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XII is further elaborated using conventional methods to provide 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XIII. For example, a compound of Formula XII can react with an acid chloride of Formula $R_4C(O)Cl$ to provide a compound of Formula XIII in which -Q-R_4 is -C(O)-R_4. In addition, a compound of Formula XII can react with sulfonyl chloride of Formula $R_4S(O)_2Cl$ or a sulfonic anhydride of Formula $(R_4S(O)_2)_2O$ to provide a compound of Formula XIII in which -Q-R_4 is -$S(O)_2$-R_4. Numerous acid chlorides of Formula $R_4C(O)Cl$, sulfonyl chlorides of Formula $R_4S(O)_2Cl$, and sulfonic anhydrides of Formula $(R_4S(O)_2)_2O$ are commercially available; others can be readily prepared using known synthetic methods. The reaction is conveniently carried out by adding the acid chloride of Formula $R_4C(O)Cl$, sulfonyl chloride of Formula $R_4S(O)_2Cl$, or sulfonic anhydride of

Formula $(R_4S(O)_2)_2O$ to a solution of the compound of Formula XII in a suitable solvent such as chloroform, dichloromethane, or 1-methyl-2-pyrrolidinone. Optionally a base such as triethylamine, pyridine, or *N,N*-diisopropylethylamine, or a combination thereof can be added. The reaction can be carried out at room temperature or initially at a sub-ambient temperature such as 0 °C and then warming to room temperature. Ureas of Formula XIII, where -Q-R_4 is -C(R_6)-NH-R_4 and R_6 is =O can be prepared by reacting a compound of Formula XII with isocyanates of Formula R_4N=C=O. Numerous isocyanates of Formula R_4N=C=O are commercially available; others can be readily prepared using known synthetic methods. The reaction can be conveniently carried out by adding the isocyanate of Formula R_4N=C=O to a solution of a compound of Formula XII in a suitable solvent such as dichloromethane or chloroform. Optionally a base such as triethylamine can be added. The reaction can be carried out at room temperature or initially at a sub-ambient temperature such as 0 °C and then warming to room temperature.

In step (2) of Reaction Scheme III, an ether substituted 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XIII is cleaved to provide a hydroxyalkyl substituted 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XIV, which is a subgenus of Formula I, using the method described in Reaction Scheme I.

Reaction Scheme III

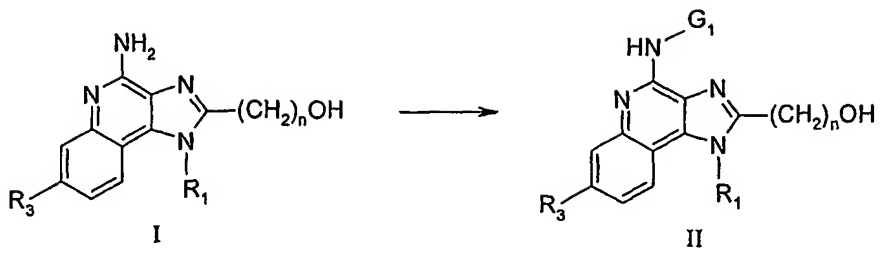


In some embodiments, compounds of the invention can be prepared according to Reaction Scheme IV, wherein R_1, R_3, G_1, and n are as defined above. Compounds of

Formula I can be prepared according to the methods described above. The amino group of a compound of Formula I can be converted by conventional methods to a functional group such as an amide, carbamate, urea, amidine, or another hydrolyzable group. A compound of this type can be made by the replacement of a hydrogen atom in an amino group with a group such as -C(O)-R', α-aminoacyl, α-aminoacyl-α-aminoacyl, -C(O)-O-R', -C(O)-N(R")R', -C(=NY')-R', -CH(OH)-C(O)-OY', -CH(OC_{1-4} alkyl)Y_0, -CH_2Y_1, and -$CH(CH_3)Y_1$; wherein R' and R" are independently selected from the group consisting of C_{1-10} alkyl, C_{3-7} cycloalkyl, phenyl, benzyl, and 2-phenylethyl, each of which may be unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, hydroxy, nitro, cyano, carboxy, C_{1-6} alkyl, C_{1-4} alkoxy, aryl, heteroaryl, aryl-C_{1-4} alkylenyl, heteroaryl-C_{1-4} alkylenyl, halo-C_{1-4} alkylenyl, halo-C_{1-4} alkoxy, -O-C(O)-CH_3, -C(O)-O-CH_3, -C(O)-NH_2, -O-CH_2-C(O)-NH_2, -NH_2, and –$S(O)_2$-NH_2, with the proviso that R" can also be hydrogen; each α-aminoacyl is an α-aminoacyl group derived from an α-amino acid selected from the group consisting of racemic, D-, and L-amino acids; Y' is selected from the group consisting of hydrogen, C_{1-6} alkyl, and benzyl; Y_0 is selected from the group consisting of C_{1-6} alkyl, carboxy-C_{1-6} alkylenyl, amino-C_{1-4} alkylenyl, mono-*N*-C_{1-6} alkylamino-C_{1-4} alkylenyl, and di-*N,N*-C_{1-6} alkylamino-C_{1-4} alkylenyl; and Y_1 is selected from the group consisting of mono-*N*-C_{1-6} alkylamino, di-*N,N*-C_{1-6} alkylamino, morpholin-4-yl, piperidin-1-yl, pyrrolidin-1-yl, and 4-C_{1-4} alkylpiperazin-1-yl. Particularly useful compounds of Formula II are amides derived from carboxylic acids containing one to ten carbon atoms, amides derived from amino acids, and carbamates containing one to ten carbon atoms. The reaction can be carried out, for example, by combining a compound of Formula I with a chloroformate or acid chloride, such as ethyl chloroformate or acetyl chloride, in the presence of a base such as triethylamine in a suitable solvent such as dichloromethane at ambient temperature.

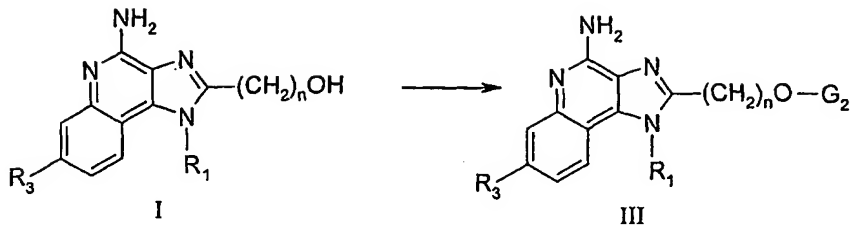
Alternatively, the hydroxy group on a compound of Formula I can be protected using a suitable silyl group such as *tert*-butyl dimethylsilyl using conventional methods. The G_1 group may then be installed using conventional methods followed by the removal of the hydroxy protecting group under acidic conditions to provide a compound of Formula II.

Reaction Scheme IV



In some embodiments, compounds of the invention can be prepared according to Reaction Scheme V, wherein R_1, R_3, G_2, and n are as defined above. Compounds of Formula I can be prepared according to the methods described above. The hydrogen atom of the alcohol group of a compound of Formula I can be replaced using conventional methods with a group such as X_2-C(O)-R', α-aminoacyl, α-aminoacyl-α-aminoacyl, -X_2-C(O)-O-R', and -C(O)-N(R")R'; wherein X_2 is selected from the group consisting of a bond; -CH_2-O-; -$CH(CH_3)$-O-; -$C(CH_3)_2$-O-; and, in the case of -X_2-C(O)-O-R', -CH_2-NH-; R' and R" are independently selected from the group consisting of C_{1-10} alkyl, C_{3-7} cycloalkyl, phenyl, benzyl, and 2-phenylethyl, each of which may be unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, hydroxy, nitro, cyano, carboxy, C_{1-6} alkyl, C_{1-4} alkoxy, aryl, heteroaryl, aryl-C_{1-4} alkylenyl, heteroaryl-C_{1-4} alkylenyl, halo-C_{1-4} alkylenyl, halo-C_{1-4} alkoxy, -O-C(O)-CH_3, -C(O)-O-CH_3, -C(O)-NH_2, -O-CH_2-C(O)-NH_2, -NH_2, and –$S(O)_2$-NH_2, with the proviso that R" can also be hydrogen; and each α-aminoacyl is an α-aminoacyl group derived from an α-amino acid selected from the group consisting of racemic, D-, and L-amino acids. Particularly useful compounds of Formula III are esters made from carboxylic acids containing one to six carbon atoms, unsubstituted or substituted benzoic acid esters, or esters made from naturally occurring amino acids. For example, the reaction can be carried out by treating a compound of Formula I with a carboxylic acid or amino acid under Mitsunobu reaction conditions by adding triphenylphosphine and a carboxylic acid to a solution or suspension of a compound of Formula I in a suitable solvent such as tetrahydrofuran and then slowly adding diisopropyl azodicarboxylate. The reaction can be run at a sub-ambient temperature such as 0 °C.

Reaction Scheme V



In some embodiments, compounds of the invention can also be prepared using the synthetic methods described in the EXAMPLES below.

Pharmaceutical Compositions and Biological Activity

Pharmaceutical compositions of the invention contain a therapeutically effective amount of a compound or salt described above in combination with a pharmaceutically acceptable carrier.

The terms "a therapeutically effective amount" and "effective amount" mean an amount of the compound or salt sufficient to induce a therapeutic or prophylactic effect, such as cytokine induction, immunomodulation, antitumor activity, and/or antiviral activity. Cytokine induction can include preferentially inducing the biosynthesis of IFN-α. The exact amount of compound or salt used in a pharmaceutical composition of the invention will vary according to factors known to those of skill in the art, such as the physical and chemical nature of the compound or salt, the nature of the carrier, and the intended dosing regimen.

In some embodiments, the compositions of the invention will contain sufficient active ingredient or prodrug to provide a dose of about 100 nanograms per kilogram (ng/kg) to about 50 milligrams per kilogram (mg/kg), preferably about 10 micrograms per kilogram (μg/kg) to about 5 mg/kg, of the compound or salt to the subject.

In other embodiments, the compositions of the invention will contain sufficient active ingredient or prodrug to provide a dose of, for example, from about 0.01 mg/m^2 to about 5.0 mg/m^2, computed according to the Dubois method, in which the body surface area of a subject (m^2) is computed using the subject's body weight: $m^2 = (wt\ kg^{0.425} \times height\ cm^{0.725}) \times 0.007184$, although in some embodiments the methods may be performed by administering a compound or salt or composition in a dose outside this range. In some of these embodiments, the method includes administering sufficient compound to provide

a dose of from about 0.1 mg/m^2 to about 2.0 mg/ m^2 to the subject, for example, a dose of from about 0.4 mg/m^2 to about 1.2 mg/m^2.

A variety of dosage forms may be used, such as tablets, lozenges, capsules, parenteral formulations (e.g., intravenous formulations), syrups, creams, ointments, aerosol formulations, transdermal patches, transmucosal patches and the like. These dosage forms can be prepared with conventional pharmaceutically acceptable carriers and additives using conventional methods, which generally include the step of bringing the active ingredient into association with the carrier.

The compounds or salts of the invention can be administered as the single therapeutic agent in the treatment regimen, or the compounds or salts described herein may be administered in combination with one another or with other active agents, including additional immune response modifiers, antivirals, antibiotics, antibodies, proteins, peptides, oligonucleotides, etc.

Compounds or salts of the invention have been shown to induce the production of certain cytokines in experiments performed according to the tests set forth below. These results indicate that the compounds or salts are useful for modulating the immune response in a number of different ways, rendering them useful in the treatment of a variety of disorders. The compounds or salts of the invention are especially useful as immune response modifiers due to their ability to preferentially induce interferon-α, thus providing a benefit over compounds that also induce pro-inflammatory cytokines (e.g. TNF-α) or that induce pro-inflammatory cytokines at higher levels. While interferon-α and pro-inflammatory cytokines are beneficial in treating certain conditions, interferon-α preferentially induced is believed to be better tolerated by patients, because the significantly lower levels of pro-inflammatory cytokines can result in fewer or less severe adverse side effects experienced by patients. For example, if a subject is treated for a disease (e.g., hepatitis C, metastatic cancer) with a compound that induces significant levels of pro-inflammatory cytokines, while treating the disease, the compound may also cause side effects, such as severe and/or widespread inflammation, tissue destruction, or emesis, that render the subject unable or unwilling to receive the treatment. Alternatively, if a subject is treated with a compound that preferentially induces interferon-α then the compound may treat the disease with less risk of adverse side effects from pro-inflammatory cytokines such as TNF-α. Therefore, by maintaining the ability to treat a

condition and reducing adverse side effects, compounds that preferentially induce IFN-α provide an advantage over compounds that would also induce pro-inflammatory cytokines, such as TNF-α, at higher levels.

The ability of the compounds or salts of the invention to preferentially induce the biosynthesis of IFN-α may be particularly advantageous when administered systemically, since adverse side effects, including for example widespread inflammation, may be reduced or even eliminated. Compounds of the invention may be administered systemically in a number of ways, including but not limited to oral and intravenous administration.

Cytokines whose biosynthesis may be induced by compounds or salts of the invention include IFN-α, IP-10, MCP-1, and a variety of other cytokines. In some instances, cytokines such as TNF-α, IL-12 may be induced, albeit at significantly reduced levels. Among other effects, these and other cytokines can inhibit virus production and tumor cell growth, making the compounds or salts useful in the treatment of viral diseases and neoplastic diseases. Accordingly, the invention provides a method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt of the invention to the animal. The animal to which the compound or salt is administered for induction of cytokine biosynthesis may have a disease as described *infra*, for example a viral disease or a neoplastic disease, and administration of the compound or salt may provide therapeutic treatment. Alternatively, the compound or salt may be administered to the animal prior to the animal acquiring the disease so that administration of the compound or salt may provide a prophylactic treatment.

In addition to the ability to induce the production of cytokines, compounds or salts of the invention can affect other aspects of the innate immune response. For example, the compounds or salts may cause maturation of dendritic cells or proliferation and differentiation of B-lymphocytes.

Whether for prophylaxis or therapeutic treatment of a disease, and whether for effecting innate or acquired immunity, the compound or salt or composition may be administered alone or in combination with one or more active components as in, for example, a vaccine adjuvant. When administered with other components, the compound or salt or composition and other component or components may be administered separately; together but independently such as in a solution; or together and associated

with one another such as (a) covalently linked or (b) non-covalently associated, e.g., in a colloidal suspension.

Conditions for which compounds or salts or compositions identified herein may be used as treatments include, but are not limited to:

(a) viral diseases such as, for example, diseases resulting from infection by an adenovirus, a herpesvirus (e.g., HSV-I, HSV-II, CMV, or VZV), a poxvirus (e.g., an orthopoxvirus such as variola or vaccinia, or molluscum contagiosum), a picornavirus (e.g., rhinovirus or enterovirus), an orthomyxovirus (e.g., influenzavirus), a paramyxovirus (e.g., parainfluenzavirus, mumps virus, measles virus, and respiratory syncytial virus (RSV)), a coronavirus (e.g., SARS), a papovavirus (e.g., papillomaviruses, such as those that cause genital warts, common warts, or plantar warts), a hepadnavirus (e.g., hepatitis B virus), a flavivirus (e.g., hepatitis C virus or Dengue virus), or a retrovirus (e.g., a lentivirus such as HIV);

(b) bacterial diseases such as, for example, diseases resulting from infection by bacteria of, for example, the genus Escherichia, Enterobacter, Salmonella, Staphylococcus, Shigella, Listeria, Aerobacter, Helicobacter, Klebsiella, Proteus, Pseudomonas, Streptococcus, Chlamydia, Mycoplasma, Pneumococcus, Neisseria, Clostridium, Bacillus, Corynebacterium, Mycobacterium, Campylobacter, Vibrio, Serratia, Providencia, Chromobacterium, Brucella, Yersinia, Haemophilus, or Bordetella;

(c) other infectious diseases, such as chlamydia, fungal diseases including but not limited to candidiasis, aspergillosis, histoplasmosis, cryptococcal meningitis, or parasitic diseases including but not limited to malaria, pneumocystis carnii pneumonia, leishmaniasis, cryptosporidiosis, toxoplasmosis, and trypanosome infection;

(d) neoplastic diseases, such as intraepithelial neoplasias, cervical dysplasia, actinic keratosis, basal cell carcinoma, squamous cell carcinoma, renal cell carcinoma, Kaposi's sarcoma, melanoma, leukemias including but not limited to acute myeloid leukemia, acute lymphocytic leukemia, chronic myeloid leukemia, chronic lymphocytic leukemia, multiple myeloma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, B-cell lymphoma, and hairy cell leukemia, and other cancers;

(e) T_H2-mediated, atopic diseases, such as atopic dermatitis or eczema, eosinophilia, asthma, allergy, allergic rhinitis, and Ommen's syndrome;

(f) certain autoimmune diseases such as systemic lupus erythematosus, essential thrombocythaemia, multiple sclerosis, discoid lupus, alopecia areata; and

(g) diseases associated with wound repair such as, for example, inhibition of keloid formation and other types of scarring (e.g., enhancing wound healing, including chronic wounds).

Additionally, a compound or salt identified herein may be useful as a vaccine adjuvant for use in conjunction with any material that raises either humoral and/or cell mediated immune response, such as, for example, live viral, bacterial, or parasitic immunogens; inactivated viral, tumor-derived, protozoal, organism-derived, fungal, or bacterial immunogens; toxoids; toxins; self-antigens; polysaccharides; proteins; glycoproteins; peptides; cellular vaccines; DNA vaccines; autologous vaccines; recombinant proteins; and the like, for use in connection with, for example, BCG, cholera, plague, typhoid, hepatitis A, hepatitis B, hepatitis C, influenza A, influenza B, parainfluenza, polio, rabies, measles, mumps, rubella, yellow fever, tetanus, diphtheria, hemophilus influenza b, tuberculosis, meningococcal and pneumococcal vaccines, adenovirus, HIV, chicken pox, cytomegalovirus, dengue, feline leukemia, fowl plague, HSV-1 and HSV-2, hog cholera, Japanese encephalitis, respiratory syncytial virus, rotavirus, papilloma virus, yellow fever, and Alzheimer's Disease.

Compounds or salts identified herein may be particularly helpful in individuals having compromised immune function. For example, compounds or salts may be used for treating the opportunistic infections and tumors that occur after suppression of cell mediated immunity in, for example, transplant patients, cancer patients and HIV patients.

Thus, one or more of the above diseases or types of diseases, for example, a viral disease or a neoplastic disease may be treated in an animal in need thereof (having the disease) by administering a therapeutically effective amount of a compound or salt of the invention to the animal.

An animal may also be vaccinated by administering an effective amount of a compound or salt described herein, as a vaccine adjuvant. In one embodiment, there is provided a method of vaccinating an animal comprising administering an effective amount of a compound or salt described herein to the animal as a vaccine adjuvant.

An amount of a compound or salt effective to induce cytokine biosynthesis is an amount sufficient to cause one or more cell types, such as dendritic cells and B-cells to

produce an amount of one or more cytokines such as, for example, IFN-α, IP-10, and MCP-1 that is increased (induced) over a background level of such cytokines. The precise amount will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg. In other embodiments, the amount is expected to be a dose of, for example, from about 0.01 mg/m^2 to about 5.0 mg/m^2, (computed according to the Dubois method as described above) although in some embodiments the induction of cytokine biosynthesis may be performed by administering a compound or salt in a dose outside this range. In some of these embodiments, the method includes administering sufficient compound or salt or composition to provide a dose of from about 0.1 mg/m^2 to about 2.0 mg/m^2 to the subject, for example, a dose of from about 0.4 mg/m^2 to about 1.2 mg/m^2.

The invention provides a method of treating a disease which is responsive to the induction of cytokine biosynthesis, particularly the preferential induction of IFN-α, including a method of treating a viral infection in an animal and a method of treating a neoplastic disease in an animal, comprising administering an effective amount of a compound or salt or composition of the invention to the animal. An amount effective to treat or inhibit a viral infection is an amount that will cause a reduction in one or more of the manifestations of viral infection, such as viral lesions, viral load, rate of virus production, and mortality as compared to untreated control animals. The precise amount that is effective for such treatment will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg. An amount of a compound or salt effective to treat a neoplastic condition is an amount that will cause a reduction in tumor size or in the number of tumor foci. Again, the precise amount will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg. In other embodiments, the amount is expected to be a dose of, for example, from about 0.01 mg/m^2 to about 5.0 mg/m^2, (computed according to the Dubois method as described above) although in some embodiments either of these methods may be performed by administering a compound or salt in a dose outside this range. In some of these embodiments, the method includes administering sufficient compound or salt to provide a dose of from about 0.1 mg/m^2 to about 2.0 mg/m^2 to the subject, for example, a dose of from about 0.4 mg/m^2 to about 1.2 mg/m^2.

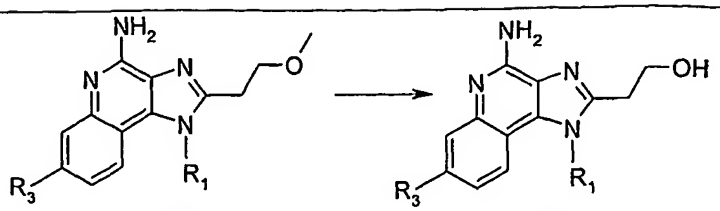
In addition to the formulations and uses described specifically herein, other formulations, uses, and administration devices suitable for compounds of the present invention are described in, for example, International Publication Nos. WO 03/077944 and WO 02/036592, U.S. Patent No. 6,245,776, and U.S. Publication Nos. 2003/0139364, 2003/185835, 2004/0258698, 2004/0265351, 2004/076633, and 2005/0009858.

Objects and advantages of this invention are further illustrated by the following examples, but the particular materials and amounts thereof recited in these examples, as well as other conditions and details, should not be construed to unduly limit this invention.

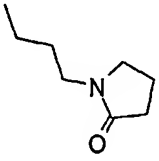
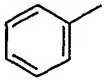
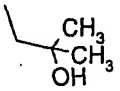
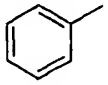
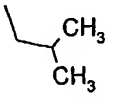
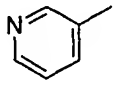
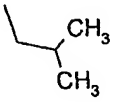
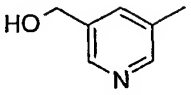
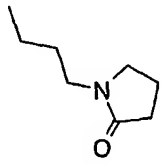
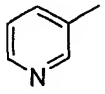
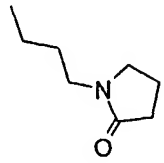
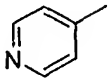
EXAMPLES

Examples 1 – 6

A solution of boron tribromide in heptane (400 μL of 1 M) was added to a tube containing a chilled (0 °C) solution of a compound of Formula Xa (about 25 mg) in dichloromethane (1 mL). The tube was vortexed, maintained at 0 °C for 0.5 hour, and then shaken overnight at ambient temperature. The reaction mixture was diluted with methanol (1 mL) and hydrochloric acid (250 μL of 6 N), vortexed, and then the solvents were removed by vacuum centrifugation. The compounds were purified by preparative high performance liquid chromatography (prep HPLC) using a Waters FractionLynx automated purification system. The prep HPLC fractions were analyzed using a Waters LC/TOF-MS, and the appropriate fractions were centrifuge evaporated to provide the trifluoroacetate salt of the desired compound. Reversed phase preparative liquid chromatography was performed with non-linear gradient elution from 5-95% B where A is 0.05% trifluoroacetic acid/water and B is 0.05% trifluoroacetic acid/acetonitrile. Fractions were collected by mass-selective triggering. Table 1 shows the structure of the starting material, a reference for the starting material, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.



Xa Ia

Example	Reference Formula Xa	R_1	R_3	Measured Mass (M+H)
1	U.S. Patent Publication 2004/0147543 Example 206			430.2227
2	U.S. Patent Publication 2004/0147543 Example 136			377.1985
3	U.S. Patent Publication 2004/0147543 Example 145			362.2008
4	U.S. Patent Publication 2004/0147543 Example 146			392.2104
5	U.S. Patent Publication 2004/0147543 Example 183			431.2209
6	U.S. Patent Publication 2004/0147543 Example 184			431.2220

Examples 7 – 31

Part A

1-(4-Amino-7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2-methylpropan-2-ol (2 g, U.S. Patent Publication 2004/0147543 Example 125) was dissolved in 7:3 volume:volume chloroform:methanol (100 mL). Aliquots (2 mL, 1.0 eq.) were added to test tubes and the solvent was removed by vacuum centrifugation. A tube

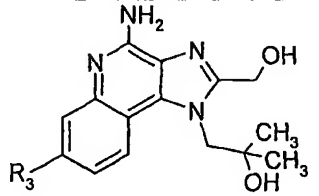
was charged with a boronic acid (1.1 eq) from the table below. *n*-Propanol (1.6 mL) was added to each tube, the tube was purged with nitrogen, and then sonicated until the contents were well mixed. Each tube was then charged sequentially with 150 μL of a solution of palladium (II) acetate in toluene (60 mg of palladium (II) acetate dissolved in 15 mL of toluene), 600 μL of 2 M aqueous sodium carbonate solution, 113 μL of water, and 53 μL of a 15 mole % solution of triphenylphosphine in *n*-propanol. The tubes were purged with nitrogen and then heated at 80 °C overnight.

The reaction mixtures were purified by solid phase extraction. Sufficient hydrochloric acid (1 N) was added to each reaction mixture to adjust the pH to <5. Each reaction mixture was loaded onto a cartridge (Waters Oasis Samples Extraction Cartridges MCX 6cc). Methanol (5 mL) was added to each cartridge. The cartridge was placed in a clean test tube. The cartridge was eluted with two successive 5 mL portions of 1 N ammonia in methanol. The solvent was removed by vacuum centrifugation.

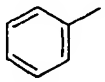
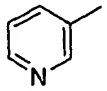
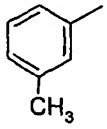
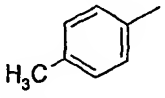
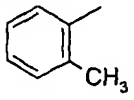
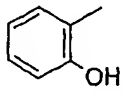
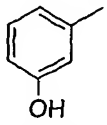
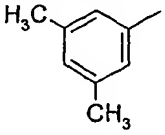
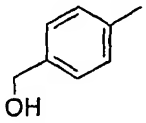
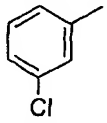
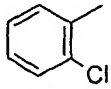
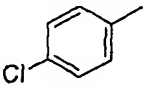
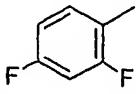
Part B

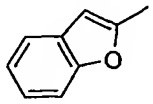
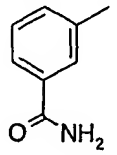
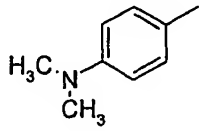
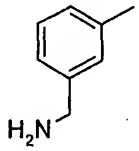
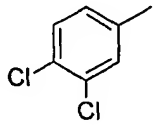
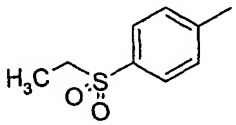
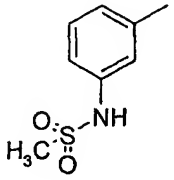
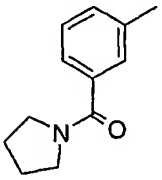
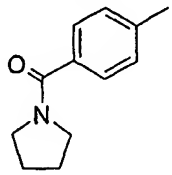
Dichloromethane (1 mL) was added to each tube, the tube was sonicated to dissolve the solids, and then the tube was chilled to 0 °C in an ice bath. A solution of boron tribromide in heptane (600 μL of 1 M) was added to each tube. The tube was vortexed, maintained at 0 °C for 0.5 hour, and then shaken overnight at ambient temperature. The solvents were removed by vacuum centrifugation. Methanol (1 mL) and hydrochloric acid (1 mL of 6 N) were added to each tube, the tubes were vortexed, and then the solvents were removed by vacuum centrifugation. The compounds were purified as described above for Examples 1 – 6. Table 2 shows the boronic acid, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

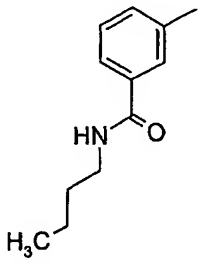
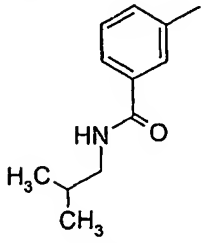
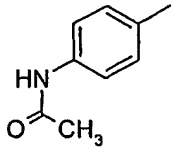
Table 2



Example	Reagent	R_3	Measured Mass (M+H)

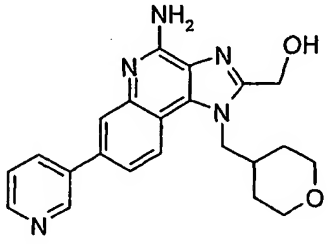
7	Phenylboronic acid		363.1847
8	Pyridine-3-boronic acid		364.1779
9	3-Methylphenylboronic acid		377.2001
10	4-Methylphenylboronic acid		377.1979
11	*o*-Tolylboronic acid		377.1990
12	(2-Hydroxyphenyl)boronic acid		379.1776
13	3-Hydroxyphenylboronic acid		379.1755
14	3,5-Dimethylphenylboronic acid		391.2130
15	4-(Hydroxymethyl)phenylboronic acid		393.1935
16	3-Chlorophenylboronic acid		397.1432
17	2-Chlorophenylboronic acid		397.1447
18	4-Chlorophenylboronic acid		397.1431
19	2,4-Difluorophenylboronic acid		399.1642

20	Benzo[b]furan-2-boronic acid		403.1812
21	(3-Aminocarbonylphenyl)boronic acid		406.1889
22	4-(*N*,*N*-Dimethylamino)phenylboronic acid		406.2255
23	(3-Aminomethylphenyl)boronic acid hydrochloride		392.2108
24	3,4-Dichlorophenylboronic acid		431.1061
25	4-(Ethylsulfonyl)phenylboronic acid		455.1771
26	3-(Methylsulfonylamino)phenylboronic acid		456.1727
27	3-(Pyrrolidine-1-carbonyl)phenylboronic acid		460.2364
28	4-(Pyrrolidine-1-carbonyl)phenylboronic acid		460.2395

29	3-(Butylaminocarbonyl)phenylboronic acid		462.2488
30	3-(Isobutylaminocarbonyl)phenylboronic acid		462.2527
31	4'-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)acetanilinde		420.2022

Example 32

[4-Amino-7-pyridin-3-yl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methanol



Part A

To a mixture of 1-tetrahydro-2*H*-pyran-4-ylmethanamine HCl (19 g, 120 mmol), dichloromethane (626 mL), and triethyl amine (43.7 mL, 313 mmol) was added 4-chloro-3-nitroquinoline at 0 °C. The resulting bright yellow solution was stirred at ambient temperature for 18 hours. The reaction was then concentrated under reduced pressure. The resulting solid was stirred in water (100 mL) and filtered to give 43 g of 7-bromo-3-nitro-*N*-(tetrahydro-2*H*-pyran-4-ylmethyl)quinolin-4-amine as a yellow powder.

Part B

7-Bromo-3-nitro-*N*-(tetrahydro-2*H*-pyran-4-ylmethyl)quinolin-4-amine (20 g, 55 mmol) was dissolved in a mixture of acetonitrile (500 mL) and isopropyl alcohol (50 mL) and the solution was placed in a pressure bottle. Platinum on carbon (5%, 2 g) was then added and the reaction mixture was shaken under H_2 at 48 PSI (3.3×10^5 Pa). After 2 hours, the reaction mixture was filtered through a pad of CELITE filter agent. The pad was rinsed with acetonitrile and the combined filtrates were concentrated under reduced pressure to give 7-bromo-N^4-(tetrahydro-2*H*-pyran-4-ylmethyl)quinoline-3,4-diamine which was carried forward without further purification assuming quantitative yield.

Part C

Chloroacetyl chloride (5.2 mL, 65 mmol) was added to 7-bromo-N^4-(tetrahydro-2*H*-pyran-4-ylmethyl)quinoline-3,4-diamine (55 mmol) dissolved in 273 mL of dichloromethane at 0 °C. A solid formed after adding half of the chloroacetyl chloride at which point additional dichloromethane (100 mL) was added. The reaction was stirred for 1 hour at ambient temperature. The yellow suspension was quenched first with aqueous saturated sodium bicarbonate followed by 50% aqueous sodium hydroxide until a pH of 14 was reached. Filtration provided 10 g of *N*-{7-bromo-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]quinolin-3-yl}-2-chloroacetamide as a tan solid. The filtrate was placed in a separatory funnel and the layers were separated. The aqueous layer was extracted with additional dichloromethane. The combined organic extracts were combined, dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford additional *N*-{7-bromo-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]quinolin-3-yl}-2-chloroacetamide as a yellow oil. The yellow oil was carried forward without further purification assuming a 50% yield (27.3 mmol). The oil was combined with ethanol (100 mL) and triethylamine (7.5 mL, 54 mmol). The resulting yellow solution was refluxed for 2 hours. The reaction was cooled to ambient temperature and the solvent was removed under reduced pressure to provide 7-bromo-2-(chloromethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline as a brown oil that was used without further purification assuming quantitative yield.

Part D

Potassium acetate (5.3 g, 55 mmol) was added to 7-bromo-2-(chloromethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline (27.3 mmol) dissolved in

dimethylformamide (100 mL). The resulting suspension was stirred at 90 °C for 1 hour. The reaction was cooled to ambient temperature and water (200 mL) was added. The aqueous layer was extracted with chloroform. The combined organic extracts were combined, dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford an orange oily solid. Chromatography (SiO_2, 0-30% 80/18/2 v/v/v $CHCl_3/CH_3OH$/concentrated NH_4OH (CMA)/$CHCl_3$) gave material that was stirred in acetonitrile and filtered to provide 2.3 g of [7-bromo-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methyl acetate as a tan solid.

Part E

3-Chloroperoxybenozic acid (2.4 g, 50% pure, 7.0 mmol) was added to a mixture of [7-bromo-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methyl acetate (2.3 g, 5.4 mmol) and chloroform (27 mL) at ambient temperature. The reaction was stirred at this temperature for 18 hours. Saturated aqueous sodium bicarbonate (50 mL) and water (50 mL) were then added to the reaction and the layers were separated. The aqueous layer was extracted with additional dichloromethane. The organic layers were combined, dried over sodium sulfate, and concentrated under reduced pressure to a dark oil. This oil was dissolved in methanol (27 mL) and to this solution was added 15 M ammonium hydroxide (3.6 mL, 54 mmol) and benzene sulfonyl chloride (2.9 mL, 23 mmol). The resulting reaction mixture was stirred at ambient temperature for 2 hours before adding additional 15 M ammonium hydroxide (3.6 mL, 54 mmol) and benzene sulfonyl chloride (2.9 mL, 23 mmol). The reaction was stirred 18 hours. The reaction was then concentrated under reduced pressure and diluted with saturated aqueous sodium bicarbonate and chloroform. A suspension resulted that was filtered to afford a solid that was stirred with saturated aqueous sodium bicarbonate and filtered to give 1.1 g of [4-amino-7-bromo-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methanol as a white solid.

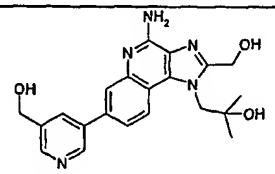
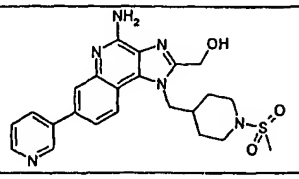
Part F

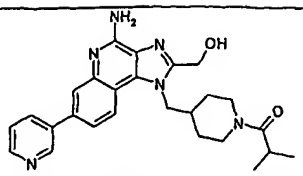
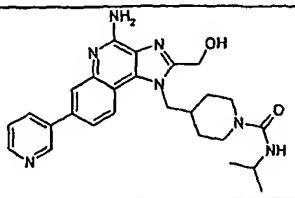
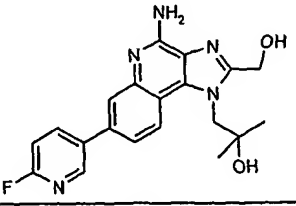
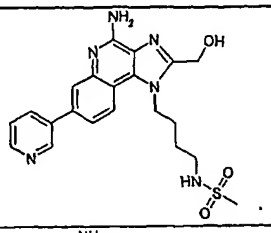
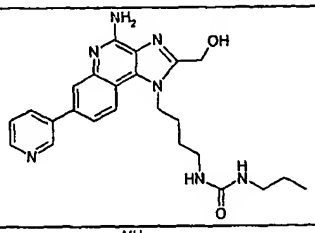
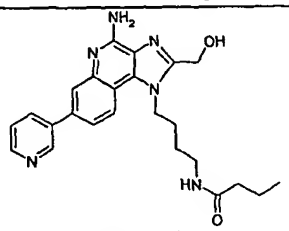
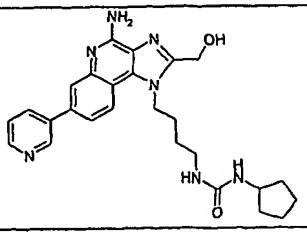
To a mixture of [4-amino-7-bromo-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methanol (500 mg, 1.28 mmol), 3-pyridyl boronic acid (233 mg, 1.90 mmol), potassium carbonate (579 mg, 4.20 mmol), dimethoxyethane (5 mL), and water (2.5 mL) under a nitrogen atmosphere was added $Pd(PPh_3)_2Cl_2$ (18 mg, 0.026 mmol). The resulting suspension was refluxed for 2 hours. The reaction was cooled to

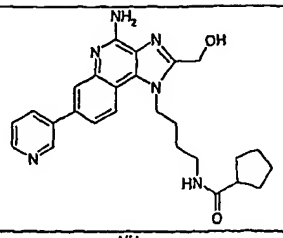
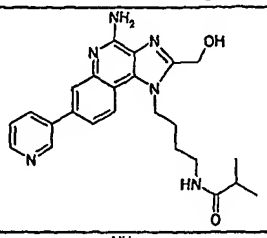
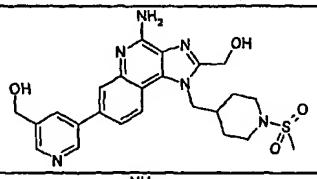
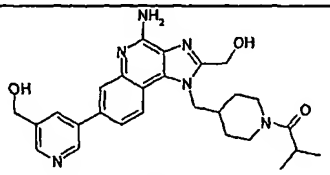
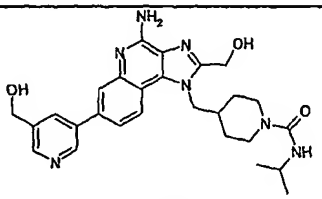
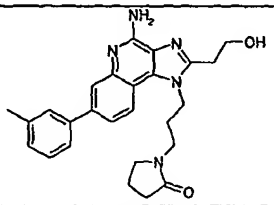
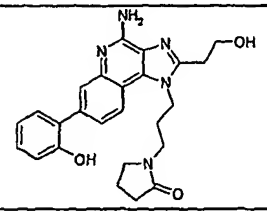
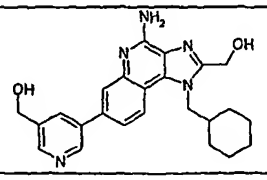
ambient temperature. The reaction mixture was diluted with chloroform and placed directly onto a silica gel column. Chromatography (SiO_2, 0-40% CMA/$CHCl_3$) gave material that was stirred in methanol and filtered to provide 263 mg of [4-amino-7-pyridin-3-yl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methanol as tan crystals, m.p. 260-262 °C. MS (APCI) *m/z* 500.3 $(M + H)^+$; Anal. calcd for $C_{22}H_{23}N_5O_2$: C, 67.85; H, 5.95; N, 17.98. Found: C, 67.49; H, 5.87; N, 17.83.

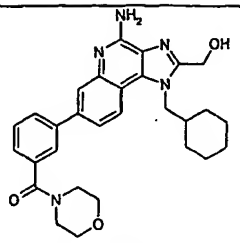
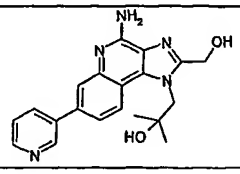
Examples 33 – 44

The compounds in the table below were prepared according to the following general procedure. The ether analog was dissolved or suspended in a solvent such as dichloromethane and the reaction mixture was stirred at 0 °C or at ambient temperature. Boron tribromide (2.5-10 equivalents, 1 M solution in dichloromethane) was added dropwise to the reaction mixture. The reaction was stirred at ambient temperature for 4 h – 6 days after which it was quenched by the careful addition of methanol or water and the solvent was removed under reduced pressure. The product was isolated by a procedure similar to that described below. The residue was combined with 2-6 M hydrochloric acid, heated to 50°C, and stirred for 1-2 hours. The resulting solution was cooled (ice bath) and then free-based (pH 9) with the addition of 2-6 M aqueous sodium hydroxide. The desired material was extracted from the aqueous using an organic solvent such as dichloromethane, ethyl acetate, or chloroform. The organic layer was separated, dried (MgSO4), filtered, and the solvent was evaporated under reduced pressure to afford the crude product. The final compound was isolated by prep HPLC (ISCO Combiflash Separation System or Analogix Purification System).

Example	Structure	Analytical Data
33		Off-white needles, mp 180-182 °C. Anal. calcd for $C_{21}H_{23}N_5O_3 \cdot 2.60H_2O$: C, 57.29; H, 6.46; N, 15.91. Found: C, 57.32; H, 6.15; N, 15.73; MS (APCI) *m/z* 394 $(M+H)^+$.
34		Off-white needles, mp 196-198 °C. Anal. calcd for $C_{23}H_{26}N_6O_3S$: C, 59.21; H, 5.62; N, 18.01. Found: C, 59.16; H, 5.84; N, 17.98; MS (APCI) *m/z* 467 $(M+H)^+$.

35		Off-white needles, mp 154-157 °C. Anal. calcd for $C_{26}H_{30}N_6O_2 \cdot 0.25H_2O$: C, 67.44; H, 6.64; N, 18.15. Found: C, 67.48; H, 6.55; N, 18.00; MS (APCI) *m/z* 459 $(M+H)^+$.
36		Off-white needles, mp 182-184 °C. Anal. calcd for $C_{26}H_{31}N_7O_2$: C, 65.94; H, 6.60; N, 20.70. Found: C, 65.70; H, 6.49; N, 20.39); MS (APCI) *m/z* 474 $(M+H)^+$.
37		Beige needles, mp 111-114 °C. Anal. calcd for $C_{20}H_{20}FN_5O_2 \cdot 2.0\ H_2O$: C, 57.55; H, 5.79; N,16.78. Found: C,57.33; H, 5.57; N, 16.76 MS (APCI) *m/z* 382 $(M+H)^+$
38		Off-white solid, mp 188-190 °C Anal. calcd for $C_{21}H_{24}N_6O_3S \cdot 1.70H_2O$ C: 53.53, H: 5.86, N: 17.84. Found: C: 53.23, %H: 5.62, N: 17.81. MS (APCI) *m/z* 459 $(M+H)^+$
39		Green solid, mp 206-209 °C Anal. calcd for $C_{24}H_{29}N_7O_2 \cdot 0.27H_2O$ C: 63.72, H: 6.58, N: 21.67. Found: C: 63.97, H: 6.26, N: 21.64. MS (APCI) *m/z* 448 $(M+H)^+$
40		Off-white solid, mp 211-212 °C Anal. calcd for $C_{24}H_{28}N_6O_2 \cdot 0.25H_2O$ C: 65.96, H: 6.57, N: 19.23.Found: C: 65.52 H: 6.38, N: 19.38 MS (APCI) *m/z* 433 $(M+H)^+$
41		Yellow solid, mp 225-227 °C Anal. calcd for $C_{26}H_{31}N_7O_2 \cdot 0.38H_2O$ C: 65.00, H: 6.66, N: 20.41. Found: C: 65.26, H: 6.53, N: 20.42. MS (APCI) *m/z* 474 $(M+H)^+$

42		White solid, mp 241-242 °C Anal. calcd for $C_{26}H_{30}N_6O_2$ C: 68.10, H: 6.59, N: 18.33. Found: C: 67.85, H: 6.48, N: 18.32. MS (APCI) *m/z* 459 $(M+H)^+$
43		White solid, mp 225-227 °C Anal. calcd for $C_{24}H_{28}N_6O_2 \cdot 0.38H_2O$ C: 65.61, H: 6.60, N: 19.13. Found: C: 65.19, H: 6.74, N: 18.96. MS (APCI) *m/z* 433 $(M+H)^+$
44		White solid, mp >300 °C. Anal. calcd for $C_{24}H_{28}N_6O_4S \cdot HBr \cdot 0.2H_2O$: C, 49.61; H, 5.10; N, 14.46. Found: C, 49.26; H, 4.84; N, 14.29 MS (APCI) *m/z* 497 $(M+H)^+$
45		Tan solid, mp >300 °C. Anal. calcd for $C_{27}H_{32}N_6O_3 \cdot HBr$: C, 56.94; H, 5.84; N, 14.76. Found: C, 56.66; H, 5.69; N, 14.63. MS (APCI) *m/z* 489 $(M+H)^+$
46		Off-white solid, mp >300 °C. Anal. calcd for $C_{27}H_{33}N_7O_3 \cdot HBr$: C, 55.14; H, 5.90; N, 16.67. Found: C, 54.86; H, 5.60; N, 16.64. MS (APCI) *m/z* 504 $(M+H)^+$
47		Off white needles, mp 218-221 °C Anal. calcd for $C_{26}H_{29}N_5O_2 \cdot 1.25\ H_2O$: C, 67.00; H, 6.81; N, 15.03. Found: C, 67.04; H, 6.78, N, 14.90. MS (APCI) *m/z* 444 $(M+H)^+$
48		Off white solid, mp >250 °C Anal. calcd for $C_{25}H_{27}N_5O_3 \cdot 0.75\ H_2O$: C, 65.41; H, 6.26; N, 15.26. Found: C, 65.48; H, 6.40; N, 15.07. MS (APCI) *m/z* 446 $(M+H)^+$
49		Off-white solid, mp 166-170 °C Anal. calcd for $C_{24}H_{27}N_5O_2 \cdot 0.9\ H_2O$: C, 66.46; H, 6.69; N, 16.15. Found: C, 66.09; H, 6.73; N, 15.97. MS (APCI) *m/z* 418 $(M + H)^+$

50		Off-white solid, mp 260-264 °C Anal. calcd for $C_{29}H_{33}N_5O_3 \cdot 0.6\ H_2O \cdot 1.0$ HCl: C, 63.69; H, 6.49; N, 12.81. Found: C, 63.37; H, 6.23; N, 12.62. MS (APCI) *m/z* 500.3 $(M + H)^+$
51		Off-white needles, mp 141-143 °C Anal. calcd for $C_{20}H_{21}N_5O_2 \cdot 1.00CH_4O \cdot 1.0$ H_2O : C, 61.15 H, 6.35 N, 16.98. Found: C, 61.15 H, 6.06 N, 17.34. MS (APCI) *m/z* 364 $(M + H)^+$

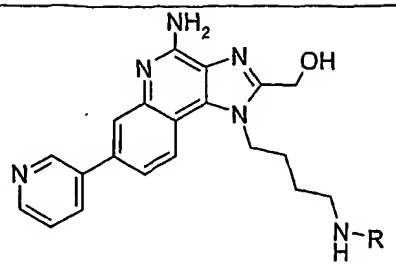
Examples 52 – 92

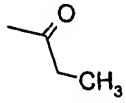
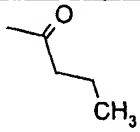
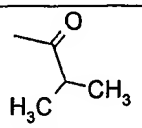
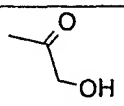
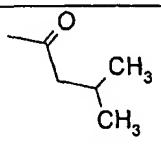
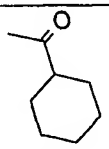
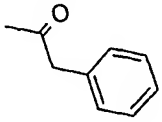
Part A

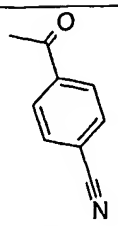
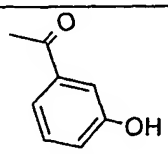
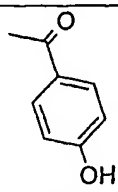
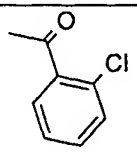
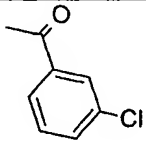
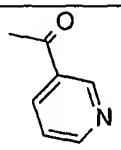
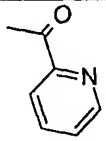
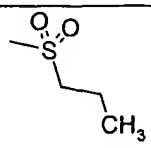
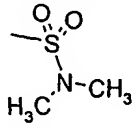
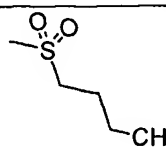
A solution of 1-(4-aminobutyl)-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinoline-4-amine (43 mg, 0.10 mmol, 1 eq, U.S. Patent Application Publication 2004/0147543, Example 372) and triethylamine (5 eq) in chloroform (1 mL) was added to a tube containing a reagent (1.1 eq) from the table below. The reaction mixture was vortexed overnight and then purified by solid-supported liquid-liquid extraction according to the following procedure. The reaction mixture was loaded onto diatomaceous earth that had been equilibrated with 1 N sodium hydroxide (600 µL) for about 20 minutes. After 10 minutes chloroform (300 µL) was added to elute the product from the diatomaceous earth into a well of a collection plate. After an additional 10 minutes the process was repeated with additional chloroform (500 µL). The solvent was then removed by vacuum centrifugation.

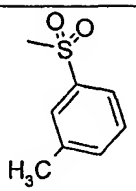
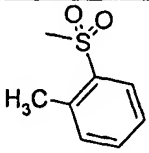
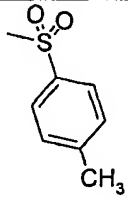
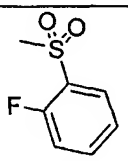
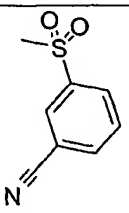
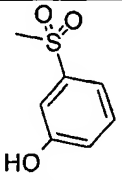
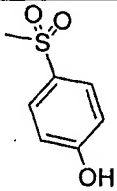
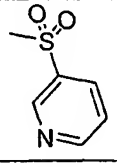
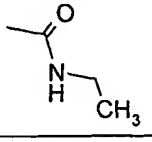
Part B

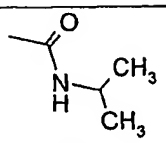
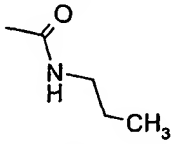
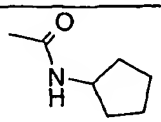
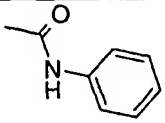
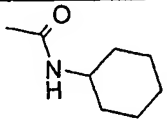
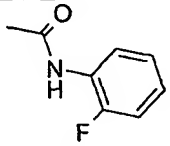
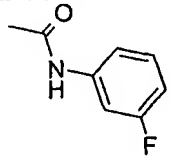
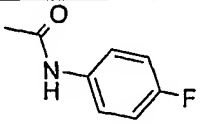
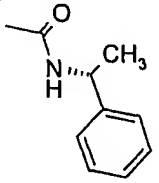
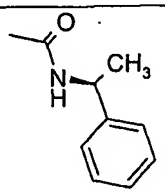
The material from Part A was dissolved in dichloromethane (600 µL) and the solution was cooled to 0 °C. Boron tribromide (400 µL of 1 M in dichloromethane) was added, the reaction mixture was vortexed, chilled for 15 minutes, and then vortexed at ambient temperature overnight. The solvent was removed by vacuum centrifugation. Methanol (300 µL) and 6 N hydrochloric acid (300 µL) were added and the reaction mixture was vortexed for 10 minutes. The solvent was removed by vacuum centrifugation. The compounds were purified as described above for Examples 1 – 6. The table below shows the reagent used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

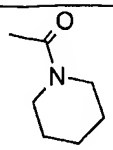
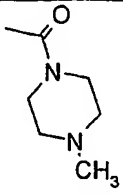


Example	Reagent	R	Measured Mass (M+H)
52	None	—H	363.1964
53	Propionyl chloride		419.2168
54	Cyclopropanecarbonyl chloride		431.2213
55	Butyryl chloride		433.2345
56	Isobutyryl chloride		433.2346
57	Methoxyacetyl chloride		421.1982
58	Cyclobutanecarbonyl chloride		445.2338
59	Isovaleryl chloride		447.2536
60	Cyclohexanecarbonyl chloride		473.2679
61	Phenylacetyl chloride		481.2368

62	4-Cyanobenzoyl chloride		492.2143
63	3-Methoxybenzoyl chloride		483.2121
64	*p*-Anisoyl chloride		483.2115
65	2-Chlorobenzoyl chloride		501.1813
66	3-Chlorobenzoyl chloride		501.1812
67	Nicotinoyl chloride hydrochloride		468.2122
68	Picolinoyl chloride hydrochloride		468.2124
69	1-Propanesulfonyl chloride		469.2039
70	Dimethylsulfamoyl chloride		470.1961
71	1-Butanesulfonyl chloride		483.2160

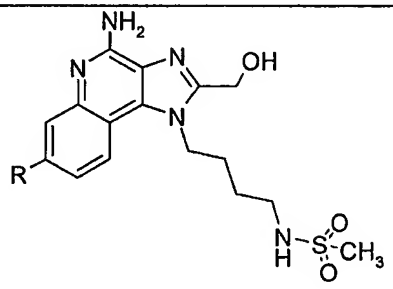
72	3-Methylbenzenesulfonyl chloride		517.2044
73	*o*-Toluenesulfonyl chloride		517.2071
74	*p*-Toluenesulfonyl chloride		517.2020
75	2-Fluorobenzenesulfonyl chloride		521.1786
76	3-Cyanobenzenesulfonyl chloride		528.1805
77	3-Methoxybenzenesulfonyl chloride		519.1829
78	4-Methoxybenzenesulfonyl chloride		519.1799
79	3-Pyridinesulfonyl chloride hydrochloride		504.1852
80	Ethyl isocyanate		434.2307

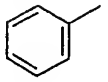
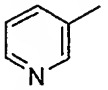
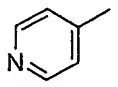
81	Isopropyl isocyanate		448.2498
82	*n*-Propyl isocyanate		448.2448
83	Cyclopentyl isocyanate		474.2629
84	Phenyl isocyanate		482.2338
85	Cyclohexyl isocyanate		488.2759
86	2-Fluorophenyl isocyanate		500.2209
87	3-Fluorophenyl isocyanate		500.2206
88	4-Fluorophenyl isocyanate		500.2209
89	(*R*)-(+)-*alpha*-Methylbenzyl isocyanate		510.2580
90	(*S*)-(-)-*alpha*-Methylbenzyl isocyanate		510.2588

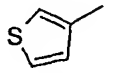
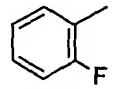
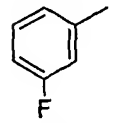
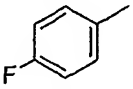
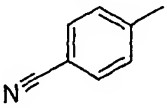
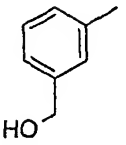
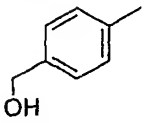
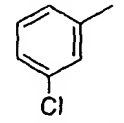
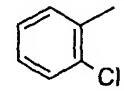
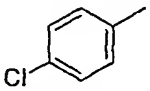
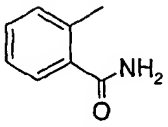
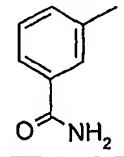
91	1-Piperidinecarbonyl chloride		474.2606
92	4-Methyl-1-piperazinecarbonyl chloride		489.2725

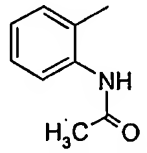
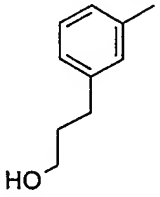
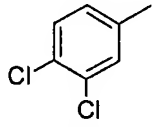
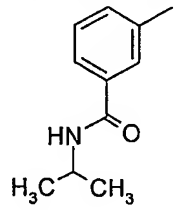
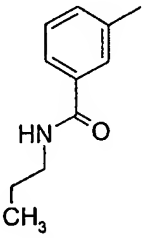
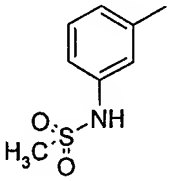
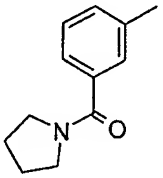
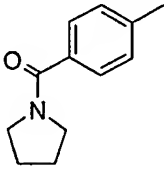
Examples 93 – 119

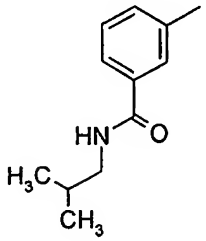
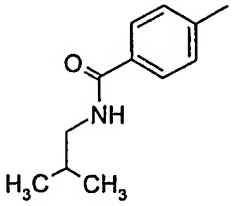
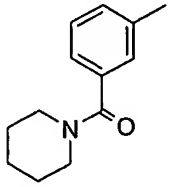
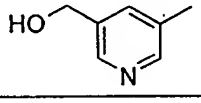
The compounds in the table below were prepared and purified according to the general method of Examples 7 – 31 using *N*-{4-[4-amino-7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}methanesulfonamide (U.S. Patent Application Publication 2004/0147543, Example 612) in lieu of 1-(4-amino-7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2-methylpropan-2-ol. Prior to purification by solid phase extraction, the reaction mixture for Example 119 was combined with water (500 µL), glacial acetic acid (500 µL), and tetrahydrofuran (500 µL) and then heated at 60 °C for 2 hours. The table below shows the boronic acid, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.



Example	Reagent	R	Measured Mass (M+H)
93	Phenylboronic acid		440.1745
94	Pyridine-3-boronic acid		441.1745
95	Pyridine-4-boronic acid		441.1679

96	Thiophene-3-boronic acid		446.1307
97	2-Fluorophenylboronic acid		458.1668
98	3-Fluorophenylboronic acid		458.1671
99	4-Fluorophenylboronic acid		458.1674
100	4-Cyanophenylboronic acid		465.1684
101	3-(Hydroxymethyl)phenylboronic acid		470.1882
102	4-(Hydroxymethyl)phenylboronic acid		470.1909
103	3-Chlorophenylboronic acid		474.1408
104	2-Chlorophenylboronic acid		474.1366
105	4-Chlorophenylboronic acid		474.1384
106	(2-Aminocarbonylphenyl)boronic acid		483.1796
107	(3-Aminocarbonylphenyl)boronic acid		483.1812

108	(2-Acetylaminophenyl)boronic acid		497.1938
109	[3-(3-Hydroxypropyl)phenyl]boronic acid		498.2136
110	3,4-Dichlorophenylboronic acid		508.0989
111	3-(*N*-Isopropylaminocarbonyl)phenylboronic acid		525.2331
112	3-(*N*-Propylaminocarbonyl)phenylboronic acid		525.2284
113	3-(Methylsulfonylamino)phenylboronic acid		533.1659
114	3-(Pyrrolidine-1-carbonyl)phenylboronic acid		537.2320
115	4-(Pyrrolidine-1-carbonyl)phenylboronic acid		537.2271

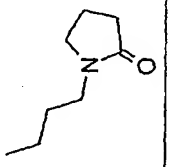
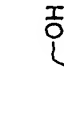
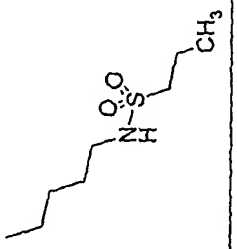
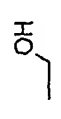
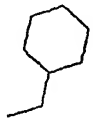
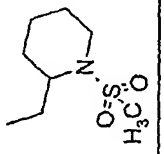
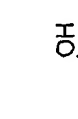
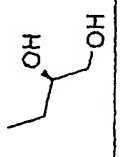
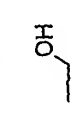
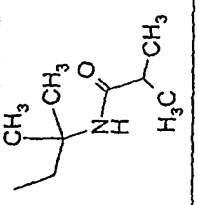
116	3-(Isobutylaminocarbonyl)phenylboronic acid		539.2418
117	4-(Isobutylaminocarbonyl)phenylboronic acid		539.2429
118	3-(Piperidine-1-carbonyl)phenylboronic acid		551.2483
119	5-*tert*-butyldimethylsilanyloxy-methyl)pyridine-3-boronic acid		471.1819

Examples 120 – 138

The compounds in the table below were prepared according to the following method. A test tube containing a solution of the corresponding ether analog (ethoxymethyl or methoxyethyl) in dichloromethane (1 mL) was cooled to 0 °C in an ice bath. Boron tribromide (4 eq of 1 M in dichloromethane) was added. The tube was vortexed, maintained at 0 °C for 0.5 hr, and then stirred at ambient temperature for 9 hours. Methanol (1 mL) and 6 N hydrochloric acid (500 μL) were added and the tube was vortexed for 5 minutes. The solvent was removed by vacuum centrifugation. The compounds were purified as described above for Examples 1 – 6. The table below shows a reference for the starting ether, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

Example	U.S. Patent Application Publication 2004/0147543	R_1	R_2	R_3	Measured Mass (M+H)
120	Example 102				347.1904
121	Example 111				372.1819
122	Example 201				440.1755
123	Example 113				348.1810
124	Example 194				458.2540

125	Example 139			470.1832
126	Example 152			466.1897
127	Example 180			502.2554
128	Example 129			460.2326
129	Example 130			476.2285

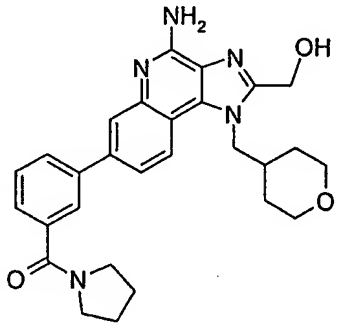
130	Example 185				460.2365
131	Example 376				469.2024
132	Example 438				388.2130
133	Example 492				467.1852
134	Example 488				366.1574
135	Example 422				433.2374

136	Example 480				482.1815
137	*				476.2383
138	Example 670				444.2371

*Although not specifically exemplified, the compound is readily prepared using the disclosed synthetic methods.

Example 139

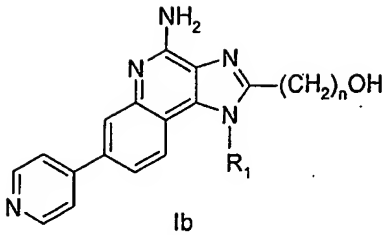
[4-Amino-7-[3-(pyrrolidin-1-ylcarbonyl)phenyl]-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methanol

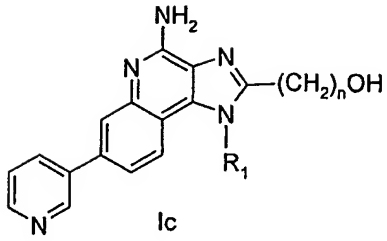


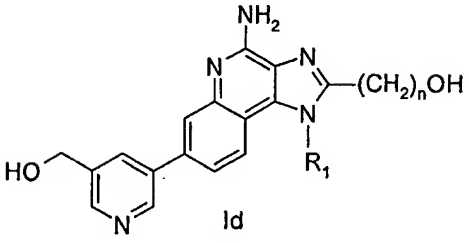
To a mixture of [4-amino-7-bromo-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-imidazo[4,5-c]quinolin-2-yl]methanol (400 mg, 1.00 mmol), 3-pyrrolidinylcarbonyl phenyl boronic acid (328 mg, 1.50 mmol), potassium carbonate (455 mg, 3.30 mmol), dimethoxyethane (4 mL), and water (2 mL) under a nitrogen atmosphere was added $Pd(PPh_3)_2Cl_2$ (14 mg, 0.02 mmol). The resulting suspension was refluxed for 18 hours. The reaction was cooled to ambient temperature. The reaction mixture was diluted with water and extracted with chloroform. The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure. Chromatography (SiO_2, 0-40% CMA/$CHCl_3$) gave material that was stirred in acetonitrile and filtered to provide 100 mg of [4-amino-7-[3-(pyrrolidin-1-ylcarbonyl)phenyl]-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methanol as a white powder, m.p. 281-284 °C. MS (APCI) *m/z* 486.3 $(M + H)^+$; Anal. calcd for $C_{28}H_{31}N_5O_3$: C, 69.26; H, 6.43; N, 14.42. Found: C, 68.99; H, 6.16; N, 14.46.

Exemplary Compounds

Certain exemplary compounds, including some of those described above in the Examples, have the following Formulas Ib, Ic, Id, Ie, If, Ig, Ih, Ii, or Ij and the following substituents n and R_1 wherein each line of the table is matched to Formula Ib, Ic, Id, Ie, If, Ig, Ih, Ii, or Ij to represent a specific embodiment of the invention.


Ib


Ic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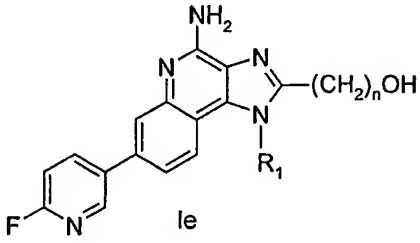
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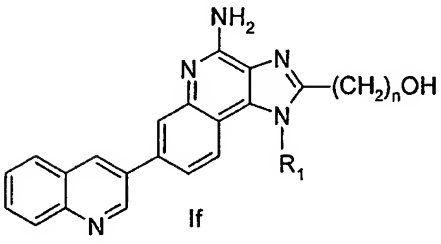
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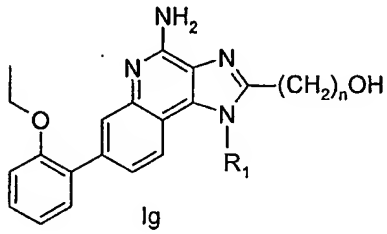
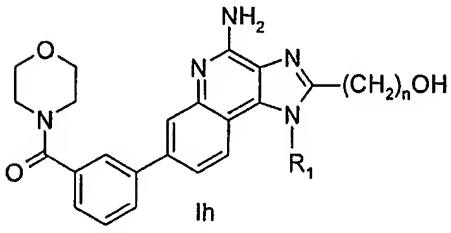

Ig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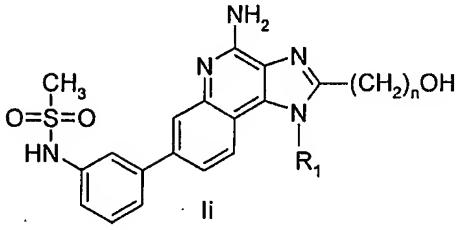
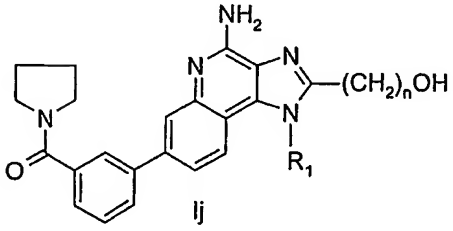

Ii


Ij

n	R_1
1	2-[(cyclohexylcarbonyl)amino]-2-methylpropyl

1	2-[(cyclopropylcarbonyl)amino]ethyl
1	4-[(cyclopropylcarbonyl)amino]butyl
1	2,3-dihydroxypropyl
1	2,2-dimethyl-3-(methylsulfonyl)propyl
1	2-fluoro-2-methylpropyl
1	2-hydroxy-2-methylpropyl
1	2-methylpropyl
1	2-methyl-2-({[(1-methylethyl)amino]carbonyl}amino)propyl
1	2-{[(1-methylethyl)carbonyl]amino}ethyl
1	4-{[(1-methylethyl)carbonyl]amino}butyl
1	2-methyl-2-[(methylsulfonyl)amino]propyl
1	4-[(methylsulfonyl)amino]butyl
1	2-[(methylsulfonyl)amino]ethyl
1	4-[(4-morpholinecarbonyl)amino]butyl
1	2-[(4-morpholinecarbonyl)amino]ethyl
1	tetrahydro-2*H*-pyran-4-ylmethyl
1	(4-hydroxytetrahydro-2*H*-pyran-4-yl)methyl
1	(1-hydroxycyclobutyl)methyl
1	(1-hydroxycyclopentyl)methyl
1	(1-hydroxycyclohexyl)methyl
2'	2-[(cyclohexylcarbonyl)amino]-2-methylpropyl
2	2-[(cyclopropylcarbonyl)amino]ethyl
2	4-[(cyclopropylcarbonyl)amino]butyl
2	2,3-dihydroxypropyl
2	2,2-dimethyl-3-(methylsulfonyl)propyl
2	2-fluoro-2-methylpropyl
2	2-hydroxy-2-methylpropyl
2	2-methylpropyl
2	2-methyl-2-({[(1-methylethyl)amino]carbonyl}amino)propyl
2	2-{[(1-methylethyl)carbonyl]amino}ethyl
2	4-{[(1-methylethyl)carbonyl]amino}butyl

2	2-methyl-2-[(methylsulfonyl)amino]propyl
2	4-[(methylsulfonyl)amino]butyl
2	2-[(methylsulfonyl)amino]ethyl
2	4-[(4-morpholinecarbonyl)amino]butyl
2	2-[(4-morpholinecarbonyl)amino]ethyl
2	tetrahydro-2*H*-pyran-4-ylmethyl
2	(4-hydroxytetrahydro-2*H*-pyran-4-yl)methyl
2	(1-hydroxycyclobutyl)methyl
2	(1-hydroxycyclopentyl)methyl
2	(1-hydroxycyclohexyl)methyl

CYTOKINE INDUCTION IN HUMAN CELLS

An in vitro human blood cell system is used to assess cytokine induction. Activity is based on the measurement of interferon (α) and tumor necrosis factor (α) (IFN-α and TNF-α, respectively) secreted into culture media as described by Testerman et. al. in "Cytokine Induction by the Immunomodulators Imiquimod and S-27609", *Journal of Leukocyte Biology, 58*, 365-372 (September, 1995).

Blood Cell Preparation for Culture

Whole blood from healthy human donors is collected by venipuncture into vacutainer tubes or syringes containing EDTA. Peripheral blood mononuclear cells (PBMC) are separated from whole blood by density gradient centrifugation using HISTOPAQUE-1077 (Sigma, St. Louis, MO) or Ficoll-Paque Plus (Amersham Biosciences Piscataway, NJ). Blood is diluted 1:1 with Dulbecco's Phosphate Buffered Saline (DPBS) or Hank's Balanced Salts Solution (HBSS). Alternately, whole blood is placed in Accuspin (Sigma) or LeucoSep (Greiner Bio-One, Inc., Longwood, FL) centrifuge frit tubes containing density gradient medium. The PBMC layer is collected and washed twice with DPBS or HBSS and re-suspended at 4 x 10^6 cells/mL in RPMI complete. The PBMC suspension is added to 96 well flat bottom sterile tissue culture plates containing an equal volume of RPMI complete media containing test compound.

Compound Preparation

The compounds are solubilized in dimethyl sulfoxide (DMSO). The DMSO concentration should not exceed a final concentration of 1% for addition to the culture wells. The compounds are generally tested at concentrations ranging from 30-0.014 μM. Controls include cell samples with media only, cell samples with DMSO only (no compound), and cell samples with reference compound.

Incubation

The solution of test compound is added at 60 μM to the first well containing RPMI complete and serial 3 fold dilutions are made in the wells. The PBMC suspension is then added to the wells in an equal volume, bringing the test compound concentrations to the desired range (usually 30-0.014 μM). The final concentration of PBMC suspension is 2 x 10^6 cells/mL. The plates are covered with sterile plastic lids, mixed gently and then incubated for 18 to 24 hours at 37°C in a 5% carbon dioxide atmosphere.

Separation

Following incubation the plates are centrifuged for 10 minutes at 1000 rpm (approximately 200 x g) at 4°C. The cell-free culture supernatant is removed and transferred to sterile polypropylene tubes. Samples are maintained at -30 to -70°C until analysis. The samples are analyzed for IFN-α by ELISA and for TNF-α by IGEN/BioVeris Assay.

Interferon (α) and Tumor Necrosis Factor (α) Analysis

IFN-α concentration is determined with a human multi-subtype colorimetric sandwich ELISA (Catalog Number 41105) from PBL Biomedical Laboratories, Piscataway, NJ. Results are expressed in pg/mL.

The TNF-α concentration is determined by ORIGEN M-Series Immunoassay and read on an IGEN M-8 analyzer from BioVeris Corporation, formerly known as IGEN International, Gaithersburg, MD. The immunoassay uses a human TNF-α capture and detection antibody pair (Catalog Numbers AHC3419 and AHC3712) from Biosource International, Camarillo, CA. Results are expressed in pg/mL.

Assay Data and Analysis

In total, the data output of the assay consists of concentration values of TNF-α and IFN-α (y-axis) as a function of compound concentration (x-axis).

Analysis of the data has two steps. First, the greater of the mean DMSO (DMSO control wells) or the experimental background (usually 20 pg/mL for IFN-α and 40 pg/mL for TNF-α) is subtracted from each reading. If any negative values result from background subtraction, the reading is reported as " * ", and is noted as not reliably detectable. In subsequent calculations and statistics, " * ", is treated as a zero. Second, all background subtracted values are multiplied by a single adjustment ratio to decrease experiment to experiment variability. The adjustment ratio is the area of the reference compound in the new experiment divided by the expected area of the reference compound based on the past 61 experiments (unadjusted readings). This results in the scaling of the reading (y-axis) for the new data without changing the shape of the dose-response curve. The reference compound used is 2-[4-amino-2-ethoxymethyl-6,7,8,9-tetrahydro-α,α-dimethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethanol hydrate (U.S. Patent No. 5,352,784; Example 91) and the expected area is the sum of the median dose values from the past 61 experiments.

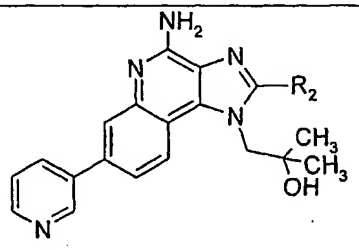
The minimum effective concentration is calculated based on the background-subtracted, reference-adjusted results for a given experiment and compound. The minimum effective concentration (μmolar) is the lowest of the tested compound concentrations that induces a response over a fixed cytokine concentration for the tested cytokine (usually 20 pg/mL for IFN-α and 40 pg/mL for TNF-α). The maximal response (pg/mL) is the maximal response attained in the dose response curve.

Compounds of the invention and close analogs were tested for their ability to induce cytokine biosynthesis using the test method described above. The analogs used are shown in the table below.

Analog	Chemical Name	Reference
1	1-(4-amino-2-ethyl-7-pyridin-3-yl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2-methylpropan-2-ol	U.S. Patent Publication 2004/0147543 Example 142
2	1-(4-amino-2-propyl-7-pyridin-3-yl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2-methylpropan-2-ol	U.S. Patent Publication 2004/0147543 Example 418
3	1-(4-amino-2-ethoxymethyl-7-pyridin-3-yl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2-methylpropan-2-ol	U.S. Patent Publication 2004/0147543 Example 126

The compound of Example 8 and several closely related analogs were tested using the test method described above. The IFN-α dose response curves are shown in Figure 1. The TNF-α dose response curves are shown in Figure 2. The minimum effective concentration for the induction of IFN-α, minimum effective concentration for the induction of TNF-α, the maximal response for IFN-α, and the maximal response for TNF-α are shown in Table 3 below where # is the number of separate experiments in which the compound was tested. When a compound was tested in more than one experiment the values shown are the median values.

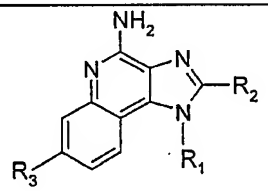
Table 3

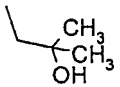
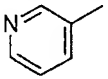
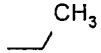
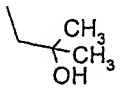
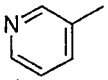
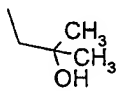
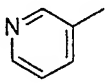
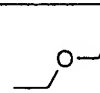
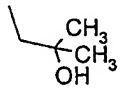
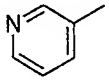
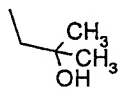
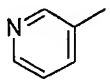
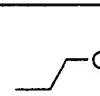
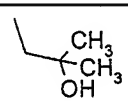
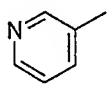


Compound	R_2	Minimum Effective Concentration (μM)		Maximal Response (pg/mL)		#
		IFN	TNF	IFN	TNF	
Example 8	$-CH_2OH$	1.11	>30	2251	*	1
Analog 1	$-CH_2CH_3$	0.12	0.37	1118	3234	4
Analog 2	$-(CH_2)_2CH_3$	0.04	0.37	597	3951	1
Analog 3	$-CH_2OCH_2CH_3$	0.04	0.12	840	7773	5

*Below experimental background level of 40 pg/mL.

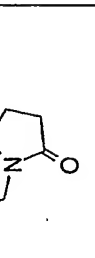
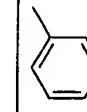
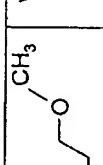
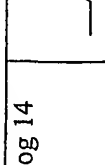
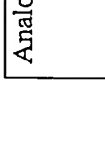
Compounds of the invention and in some instances, close analogs, were tested for their ability to induce cytokine biosynthesis using the test method described above. The minimum effective concentration for the induction of IFN-α, minimum effective concentration for the induction of TNF-α, the maximal response for IFN-α, and the maximal response for TNF-α are shown in the table below where # is the number of separate experiments in which the compound was tested. When a compound was tested in more than one experiment the values shown are the median values.

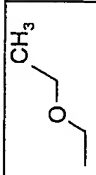
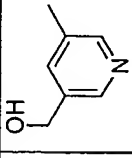
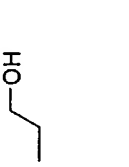
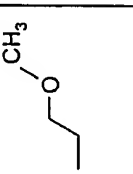
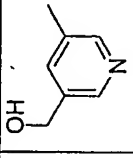
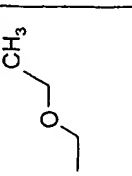
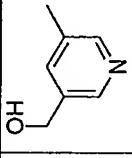
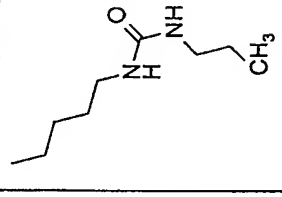


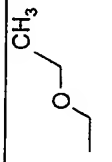
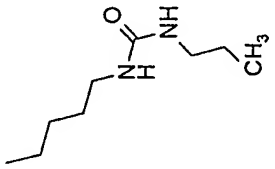
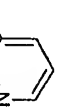
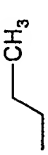
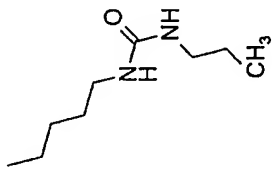
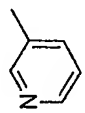
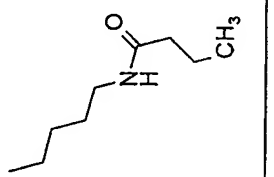
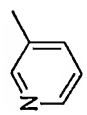
Compound	R_2	R_1	R_3	Minimum Effective Concentration (μM)		Maximal Response (pg/mL)		#
				IFN	TNF	IFN	TNF	
Example 8				0.37	10	2886	51	3
Analog 1				0.12	0.37	1652	3571	6
Analog 2				0.04	0.37	597	3951	1
Analog 3				0.04	0.12	840	7867	7
Analog 4				0.37	1.11	829	3445	4
Analog 5				0.014	0.014	1065	8386	8

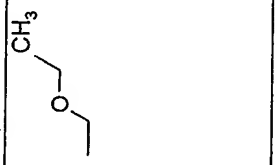
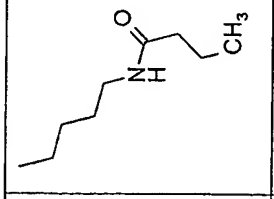
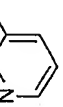
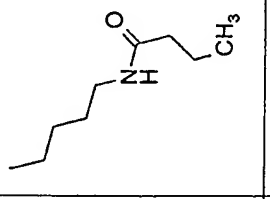
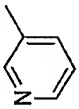
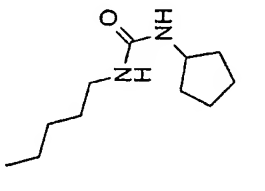
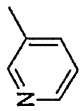
Example 33				0.37	>30	4357	*	3
Analog 6				0.12	3.33	1771	8000	4
Analog 7				0.014	0.12	6308	18284	4
Analog 8				0.014	1.11	2084	10087	5
Analog 9				0.014	0.04	5868	16296	2
Analog 10				0.014	0.12	1079	16482	2

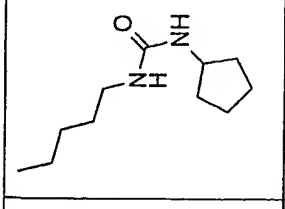
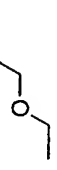
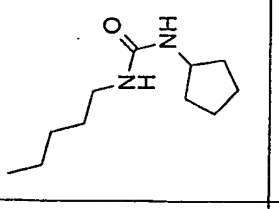
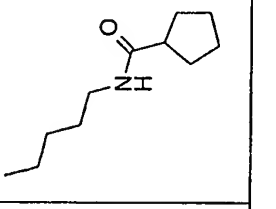
Example 35				1.11	>30	969	*	1
Analog 11				0.12	0.37	2979	1449	2
Analog 12				0.12	1.11	1686	619	8
Analog 13				0.12	0.37	1157	1054	2
Example 1				>30	>30	*	*	1

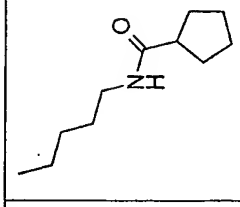
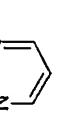
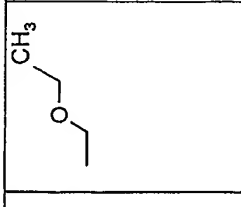
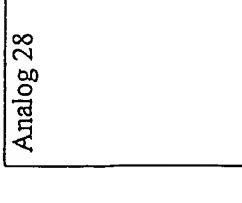
Analog 14				0.12	1.11	1880	201	2
Analog 15				0.37	1.11	1665	62	1
Example 2				0.37	3.33	1274	67	1
Analog 16				0.014	0.014	260	2296	1
Analog 17				0.014	0.12	440	2238	1
Example 3				0.37	3.33	1180	42	1
Analog 18				0.014	0.04	1199	3151	3

Analog 19			0.014	0.12	591	647	1
Example 4			0.12	10	1891	349	1
Analog 20			0.014	0.04	1332	9563	2
Analog 21			0.04	0.37	1263	3885	3
Example 39			0.37	30	5089	81	1

Analog 22				0.04	1.11	936	1059	2
Analog 23				0.37	0.37	531	5284	1
Example 40				0.12	>30	3516	*	1

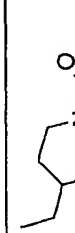
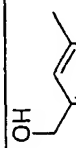
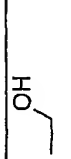
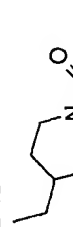
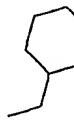
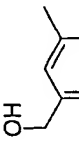
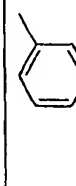
Analog 24				0.12	1.11	965	991	2
Analog 25				0.12	0.37	862	1647	2
Example 41				0.04	10	4373	600	1

Analog 26			0.014	1.11	925	1618	2
Analog 27			0.014	0.37	649	9019	1
Example 42			0.12	3.33	2745	410	1

Analog 28			0.04	0.37	969	1366	2
Analog 29			0.12	0.37	521	2222	1
Example 43			0.37	10	5880	217	1
Analog 30			0.12	1.11	1194	728	2

Analog 31				0.12	0.37	1610	960	2
Example 5				30	>30	109	*	1
Analog 32				0.12	1.11	753	380	3
Example 6				>30	>30	*	*	1
Analog 33				0.37	3.33	1179	943	3

Example 9				30	>30	87	*	1
Analog 34				0.014	0.12	541	10184	1
Example 10				0.37	0.37	1681	7423	1
Analog 35				0.12	0.12	650	4456	1
Example 13				0.37	10	12641	352	1
Analog 36				0.04	0.04	740	3955	1

Example 45				>30	>30	*	*	1
Analog 37				0.04	1.11	1382	3128	1
Example 49				3.33	>30	1087	*	1
Analog 38				0.014	1.11	1062	2865	2
Example 50				1.11	>30	1266	*	1

Analog 39				0.014	0.37	815	1054

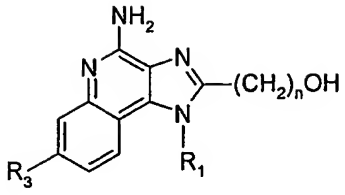
*Below experimental background level

All analogs are either specifically exemplified in or are readily prepared using the synthetic methods disclosed in U.S. Patent Application Publication 2004/0147543

The complete disclosures of the patents, patent documents, and publications cited herein are incorporated by reference in their entirety as if each were individually incorporated. Various modifications and alterations to this invention will become apparent to those skilled in the art without departing from the scope and spirit of this invention. It should be understood that this invention is not intended to be unduly limited by the illustrative embodiments and examples set forth herein and that such examples and embodiments are presented by way of example only with the scope of the invention intended to be limited only by the claims set forth herein as follows.

WHAT IS CLAIMED IS:

1. A compound of Formula I:



I

wherein:

n is 1 or 2;

R_1 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$, and

$-X-R_5$;

R_3 is selected from the group consisting of:

-Z-Ar,

$-Z-Ar'-Y-R_4$, and

$-Z-Ar'-X-Y-R_4$;

Ar is selected from the group consisting of aryl and heteroaryl both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, amino, alkylamino, and dialkylamino;

Ar' is selected from the group consisting of arylene and heteroarylene both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, amino, alkylamino, and dialkylamino;

X is alkylene optionally interrupted by one -O- group;

Y is selected from the group consisting of:

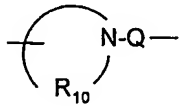
-O-,

$-C(R_6)-$,

$-C(R_6)-N(R_8)-$,

$-S(O)_{0-2}-$,

$-N(R_8)-Q-$,



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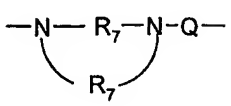
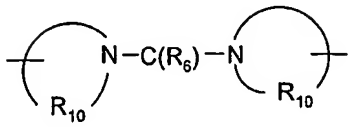


, and

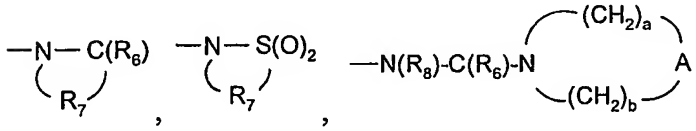


;

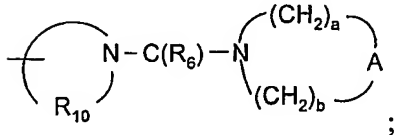
Z is selected from the group consisting of a bond and alkylene;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, and heterocyclyl, wherein the alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclyl, amino, alkylamino, dialkylamino, and, in the case of alkyl, alkenyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



, and



;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and

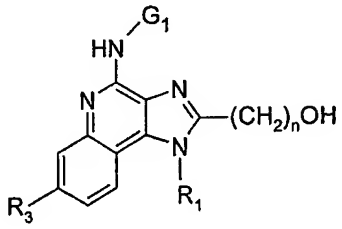
-N(Q-R_4)-;

Q is selected from the group consisting of a bond, -C(R_6)-, -S(O)$_2$, -C(R_6)-N(R_8)-, -S(O)$_2$-N(R_8)-, -C(R_6)-O-, and -C(R_6)-S-; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

or a pharmaceutically acceptable salt thereof.

2. A compound of Formula II:



II

wherein:

G_1 is selected from the group consisting of:

-C(O)-R',

α-aminoacyl,

α-aminoacyl-α-aminoacyl,

-C(O)-O-R',

-C(O)-N(R")R',

-C(=NY')-R',

-CH(OH)-C(O)-OY',

-CH(OC$_{1-4}$ alkyl)Y_0,

-CH_2Y_1, and

-$CH(CH_3)Y_1$;

R' and R" are independently selected from the group consisting of C_{1-10} alkyl, C_{3-7} cycloalkyl, phenyl, and benzyl, each of which may be unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, hydroxy, nitro, cyano, carboxy, C_{1-6} alkyl, C_{1-4} alkoxy, aryl, heteroaryl, aryl-C_{1-4} alkylenyl, heteroaryl-C_{1-4} alkylenyl, halo-C_{1-4} alkylenyl, halo-C_{1-4} alkoxy, -O-C(O)-CH_3, -C(O)-O-CH_3, -C(O)-NH_2, -O-CH_2-C(O)-NH_2, -NH_2, and –S(O)$_2$-NH_2, with the proviso that R" can also be hydrogen;

α-aminoacyl is an α-aminoacyl group derived from an α-amino acid selected from the group consisting of racemic, D-, and L-amino acids;

Y' is selected from the group consisting of hydrogen, C_{1-6} alkyl, and benzyl;

Y_0 is selected from the group consisting of C_{1-6} alkyl, carboxy-C_{1-6} alkylenyl, amino-C_{1-4} alkylenyl, mono-*N*-C_{1-6} alkylamino-C_{1-4} alkylenyl, and di-*N,N*-C_{1-6} alkylamino-C_{1-4} alkylenyl;

Y_1 is selected from the group consisting of mono-*N*-C_{1-6} alkylamino, di-*N,N*-C_{1-6} alkylamino, morpholin-4-yl, piperidin-1-yl, pyrrolidin-1-yl, and 4-C_{1-4} alkylpiperazin-1-yl;

n is 1 or 2;

R_1 is selected from the group consisting of:

-R_4,

-X-R_4,

-X-Y-R_4, and

-X-R_5;

R_3 is selected from the group consisting of:

-Z-Ar,

-Z-Ar'-Y-R_4, and

-Z-Ar'-X-Y-R_4;

Ar is selected from the group consisting of aryl and heteroaryl both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, amino, alkylamino, and dialkylamino;

Ar' is selected from the group consisting of arylene and heteroarylene both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, amino, alkylamino, and dialkylamino;

X is alkylene optionally interrupted by one -O- group;

Y is selected from the group consisting of:

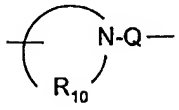
-O-,

-$C(R_6)$-,

-$C(R_6)$-$N(R_8)$-,

-$S(O)_{0-2}$-,

-$N(R_8)$-Q-,



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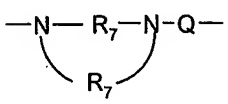
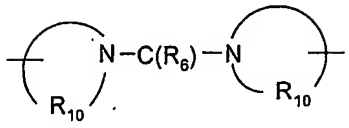


, and

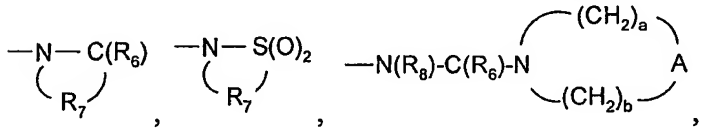


;

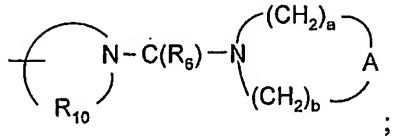
Z is selected from the group consisting of a bond and alkylene;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, and heterocyclyl, wherein the alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclyl, amino, alkylamino, dialkylamino, and, in the case of alkyl, alkenyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



, and



;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R_{10} is C_{3-8} alkylene;

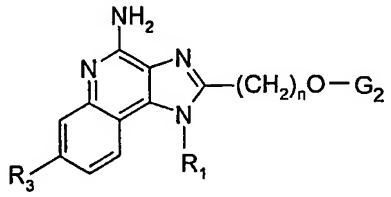
A is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(Q-R_4)-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-S(O)_2$, $-C(R_6)-N(R_8)-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-S-$; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

or a pharmaceutically acceptable salt thereof.

3. A compound of Formula III:



III

wherein:

G_2 is selected from the group consisting of:

$-X_2-C(O)-R'$,

α-aminoacyl,

α-aminoacyl-α-aminoacyl,

$-X_2-C(O)-O-R'$, and

$-C(O)-N(R'')R'$;

X_2 is selected from the group consisting of a bond; $-CH_2-O-$; $-CH(CH_3)-O-$; $-C(CH_3)_2-O-$; and, in the case of $-X_2-C(O)-O-R'$, $-CH_2-NH-$;

R' and R'' are independently selected from the group consisting of C_{1-10} alkyl, C_{3-7} cycloalkyl, phenyl, benzyl, and 2-phenylethyl, each of which may be unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, hydroxy, nitro, cyano, carboxy, C_{1-6} alkyl, C_{1-4} alkoxy, aryl, heteroaryl, aryl-C_{1-4} alkylenyl, heteroaryl-C_{1-4} alkylenyl, halo-C_{1-4} alkylenyl, halo-C_{1-4} alkoxy, $-O-C(O)-CH_3$, $-C(O)-O-CH_3$, $-C(O)-NH_2$, $-O-CH_2-C(O)-NH_2$, $-NH_2$, and $-S(O)_2-NH_2$, with the proviso that R'' can also be hydrogen;

α-aminoacyl is an α-aminoacyl group derived from an α-amino acid selected from the group consisting of racemic, D-, and L-amino acids;

n is 1 or 2;

R_1 is selected from the group consisting of:

-R_4,

-X-R_4,

-X-Y-R_4, and

-X-R_5;

R_3 is selected from the group consisting of:

-Z-Ar,

-Z-Ar'-Y-R_4, and

-Z-Ar'-X-Y-R_4;

Ar is selected from the group consisting of aryl and heteroaryl both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, amino, alkylamino, and dialkylamino;

Ar' is selected from the group consisting of arylene and heteroarylene both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, amino, alkylamino, and dialkylamino;

X is alkylene optionally interrupted by one -O- group;

Y is selected from the group consisting of:

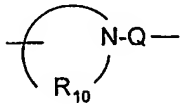
-O-,

-C(R_6)-,

-C(R_6)-N(R_8)-,

-S(O)$_{0-2}$-,

-N(R_8)-Q-,



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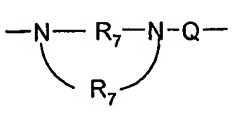

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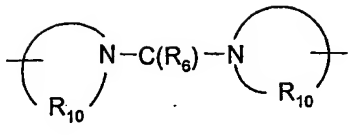
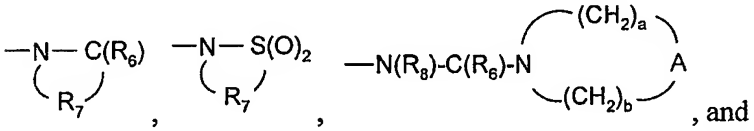
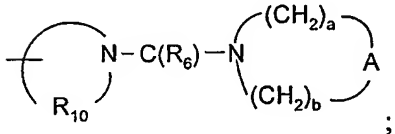

;

Z is selected from the group consisting of a bond and alkylene;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, and heterocyclyl, wherein the alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclyl, amino, alkylamino, dialkylamino, and, in the case of alkyl, alkenyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:


, and


;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(Q-R_4)-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-S-$; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

or a pharmaceutically acceptable salt thereof.

4. The compound or salt of any one of claims 1, 2, and 3 wherein n is 1.

5. The compound or salt of any one of claims 1, 2, and 3 wherein n is 2.

6. The compound or salt of any one of claims 1 through 5 wherein R_1 is selected from the group consisting of alkyl, aminoalkyl, dihydroxyalkyl, haloalkyl, and hydroxyalkyl.

7. The compound or salt of any one of claims 1 through 6 wherein R_1 is selected from the group consisting of methyl, ethyl, n-propyl, n-butyl, 2-methylpropyl, 2-amino-2-methylpropyl, 3-amino-2,2-dimethylpropyl, 2,3-dihydroxypropyl, 2-fluoro-2-methylpropyl, and 2-hydroxy-2-methylpropyl.

8. The compound or salt of any one of claims 1 through 6 wherein R_1 is selected from the group consisting of (1-hydroxycyclobutyl)methyl, (1-hydroxycyclopentyl)methyl, and (1-hydroxycyclohexyl)methyl.

9. The compound or salt of any one of claims 1 through 5 wherein R_1 is heterocyclylalkylenyl wherein heterocyclyl is unsubstituted or substituted by one or more substituents independently selected from the group consisting of C_{1-4} alkyl, hydroxy, and oxo.

10. The compound or salt of claim 9 wherein heterocyclyl is selected from the group consisting of 1,3-dioxolanyl, tetrahydropyranyl, tetrahydrofuranyl, piperidinyl, and morpholinyl, and alkylenyl is C_{1-4} alkylenyl.

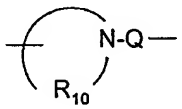
11. The compound or salt of claim 9 wherein R_1 is selected from the group consisting of tetrahydro-2*H*-pyran-4-ylmethyl and (2,2-dimethyl-1,3-dioxolan-4-yl)methyl

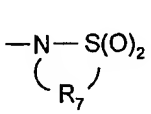
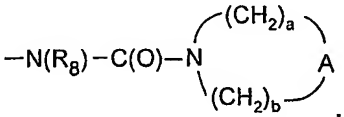
12. The compound or salt of claim 9 wherein R_1 is (4-hydroxytetrahydro-2*H*-pyran-4-yl)methyl.

13. The compound or salt of any one of claims 1 through 5 wherein R_1 is -X-Y-R_4 wherein X is C_{1-6} alkylene which may be interrupted by an -O- group; Y is selected from the group consisting of -N(R_8)-C(O)-, -N(R_8)-S(O)$_2$-, -N(R_8)-C(O)-N(R_8)-, and -S(O)$_2$-

wherein R_8 is selected from hydrogen and methyl; and R_4 is selected from the group consisting of C_{1-6} alkyl, isoquinolinyl, *N*-methylimidazolyl, pyridinyl, quinolinyl, phenyl, and phenyl substituted by a substituent selected from the group consisting of chloro, cyano, fluoro, hydroxy, and methyl.

14. The compound or salt of any one of claims 1 through 5 and 13 wherein R_1 is selected from the group consisting of 2-[(cyclopropylcarbonyl)amino]ethyl, 4-[(cyclopropylcarbonyl)amino]butyl, 2-[(cyclohexylcarbonyl)amino]-2-methylpropyl, 2-{[(1-methylethyl)carbonyl]amino}ethyl, 4-{[(1-methylethyl)carbonyl]amino}butyl, 2-methyl-2-{[(1-methylethyl)carbonyl]amino}propyl, 2-[(methylsulfonyl)amino]ethyl, 4-[(methylsulfonyl)amino]butyl, 2-methyl-2-[(methylsulfonyl)amino]propyl, 2-methyl-2-({[(1-methylethyl)amino]carbonyl}amino)propyl, 2-methyl-2-[2-(methylsulfonyl)ethoxy]propyl, and 2,2-dimethyl-3-(methylsulfonyl)propyl.

15. The compound or salt of any one of claims 1 through 5 wherein R_1 is -X-Y-R_4 wherein X is C_{1-6} alkylene which may be interrupted by an -O- group; Y is selected from the group consisting of -N(R_8)-C(O)-, -N(R_8)-S(O)$_2$-, -N(R_8)-C(O)-N(R_8)-, -N(R_8)-S(O)$_2$-N(R_8)-, -S(O)$_2$-, and  wherein Q is -C(O)-, -C(O)-NH-, or -S(O)$_2$-, R_{10} is pentylene, R_8 is hydrogen or methyl; and R_4 is selected from the group consisting of C_{1-6} alkyl, hydroxyC_{1-6} alkyl, isoquinolinyl, *N*-methylimidazolyl, pyridinyl, quinolinyl, benzyl, 1-phenylethyl, phenyl, and phenyl substituted by a substituent selected from the group consisting of chloro, cyano, fluoro, hydroxy, and methyl.

16. The compound or salt of any one of claims 1 through 5 wherein R_1 is -X-R_5 wherein X is C_{1-6} alkylene, and R_5 is  or  .

17. The compound or salt of any one of claims 1 through 5 and 16 wherein R_1 is selected from the group consisting of 4-(1,1-dioxidoisothiazolidin-2-yl)butyl, 4-[(4-morpholinecarbonyl)amino]butyl, and 2-[(4-morpholinecarbonyl)amino]ethyl.

18. The compound or salt of any one of claims 1 through 17 wherein Z is a bond.

19. The compound or salt of any one of claims 1 through 18 wherein R_3 is phenyl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, or quinolin-3-yl any of which may be unsubstituted or substituted by one or more substituents selected from the group consisting of alkyl, alkoxy, halogen, hydroxy, and hydroxyalkyl.

20. The compound or salt of claim 19 wherein R_3 is selected from the group consisting of pyridin-3-yl, pyridin-4-yl, 6-fluoropyridin-3-yl, 5-(hydroxymethyl)pyridin-3-yl, 2-ethoxyphenyl, and quinolin-3-yl.

21. The compound or salt of any one of claims 1 through 18 wherein R_3 is thien-3-yl, phenyl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, or quinolin-3-yl any of which may be unsubstituted or substituted by one or more substituents selected from the group consisting of alkyl, alkoxy, halogen, cyano, hydroxy, and hydroxyalkyl.

22. The compound or salt of any one of claims 1 through 18 wherein R_3 is -Ar'-Y-R_4 wherein Ar' is phenylene, Y is selected from the group consisting of -C(O)-, -C(O)-N(R_8)-, -N(R_8)-C(O)-, -N(R_8)-S(O)$_2$-, and -N(R_8)-C(O)-N(R_8)- wherein R_8 is selected from hydrogen and methyl; and R_4 is selected from the group consisting of C_{1-6} alkyl, morpholin-4-yl, phenyl, and phenyl substituted by a substituent selected from the group consisting of alkyl, alkoxy, halogen, hydroxy, and hydroxyalkyl.

23. The compound or salt of any one of claims 1 through 18 wherein R_3 is -Ar'-Y-R_4 wherein Ar' is phenylene, Y is selected from the group consisting of -C(O)-, -C(O)-N(R_8)-, -N(R_8)-C(O)-, -N(R_8)-S(O)$_2$-, and -N(R_8)-C(O)-N(R_8)- wherein R_8 is selected from hydrogen and methyl; and R_4 is selected from the group consisting of C_{1-6} alkyl, phenyl, and phenyl substituted by a substituent selected from the group consisting of alkyl, alkoxy, halogen, hydroxy, and hydroxyalkyl; with the proviso that when Y is -C(O)-N(R_8)- or

-N(R_8)-C(O)-N(R_8)- then R_4 can also be hydrogen; and with the further proviso that when Y is -C(O)- or -N(R_8)-C(O)- then R_4 can also be morpholin-4-yl, piperidin-1-yl, or pyrrolidin-1-yl.

24. The compound or salt of claim 23 wherein R_3 is 3-(methylsulfonylamino)phenyl, 3-(pyrrolidin-1-ylcarbonyl)phenyl, or 3-(morpholin-4-ylcarbonyl)phenyl.

25. A compound selected from the group consisting of 2-hydroxymethyl-1-(2-methylpropyl)-7-phenyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine, 2-(2-hydroxyethyl)-1-(2-methylpropyl)-7-phenyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine, 1-(4-amino-2-hydroxymethyl-7-phenyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2-methylpropan-2-ol, and 1-[4-amino-2-(2-hydroxyethyl)-7-phenyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol, or a pharmaceutically acceptable salt thereof.

26. A compound selected from the group consisting of *N*-[4-(4-amino-2-hydroxymethyl-7-phenyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]methanesulfonamide and *N*-{4-[4-amino-2-(2-hydroxyethyl)-7-phenyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl]}methanesulfonamide, or a pharmaceutically accdptable salt thereof.

27. A compound selected from the group consisting of 2-hydroxymethyl-1-(2-methylpropyl)-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine, 2-(2-hydroxyethyl)-1-(2-methylpropyl)-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine, 1-[4-amino-2-hydroxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol, and 1-[4-amino-2-(2-hydroxyethyl)-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol, or a pharmaceutically acceptable salt thereof.

28. A compound selected from the group consisting of *N*-{4-[4-amino-2-hydroxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl]}methanesulfonamide and *N*-{4-[4-amino-2-(2-hydroxyethyl)-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl]}methanesulfonamide, or a pharmaceutically acceptable salt thereof.

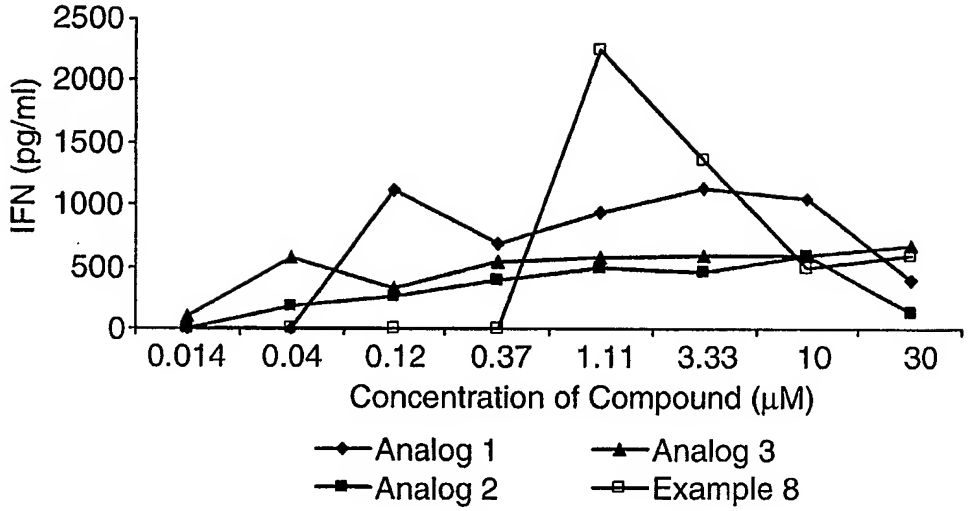
29. A pharmaceutical composition comprising a therapeutically effective amount of a compound or salt of any one of claims 1 through 28 and a pharmaceutically acceptable carrier.

30. A method of preferentially inducing the biosynthesis of IFN-α in an animal comprising administering an effective amount of a compound or salt of any one of claims 1 through 28 or a pharmaceutical composition of claim 29 to the animal.

31. A method of treating a viral disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound or salt of any one of claims 1 through 28 or the pharmaceutical composition of claim 29 to the animal.

32. A method of treating a neoplastic disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound or salt of any one of claims 1 through 28 or the pharmaceutical composition of claim 29 to the animal.

33. The method of anyone of claims 30, 31, and 32 wherein the compound or salt or pharmaceutical composition is administered systemically.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500
0
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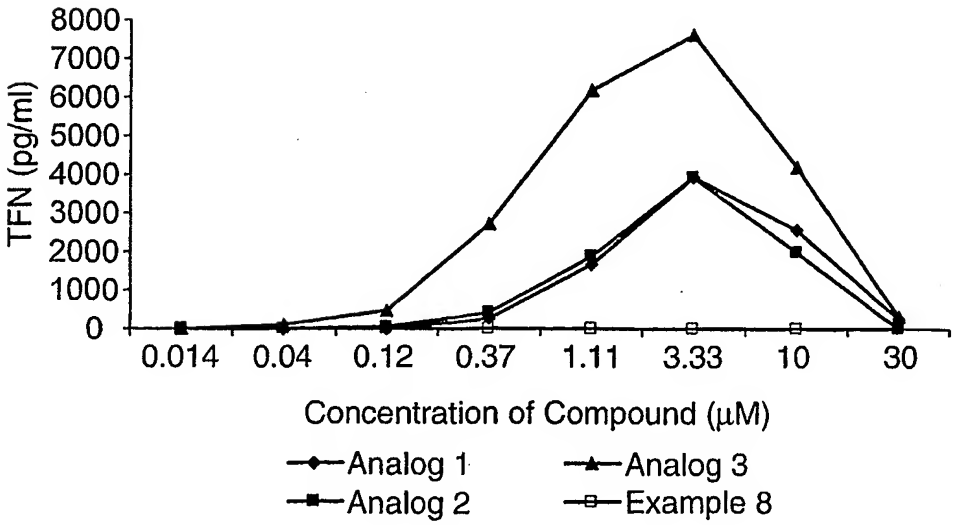
0.04
0.12
0.37
1.11
3.33
10
30
Concentration of Compound (μM)
Analog 1
Analog 3
Analog 2
Example 8

Fig. 1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5000
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3000
2000
1000
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TFN (pg/ml)
0.014
0.04
0.12
0.37
1.11
3.33
10
30
Concentration of Compound (μM)
Analog 1
Analog 3
Analog 2
Example 8

Fig. 2